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ACQUIRED ARTERIOVENOUS FISTULAS COMPLICATED BY ENDARTERITIS, AND ENDOCARDITIS LENTA DUE TO *STREPTOCOCCUS FAECALIS**

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THE occurrence of an acquired arteriovenous fistula complicated by both bacterial endocarditis and endarteritis is unusual. Although 20 cases of traumatic arteriovenous fistula with associated bacterial endarteritis have been reported,[1-20] only 7 of these were complicated by coexistent endocarditis.[1-7] The aortic valve was the site of the endocarditis in all cases. Heretofore, *Streptococcus viridans* has been found to be the cause of the septicemia. Although arteriovenous fistula with endarteritis has occurred at variable sites, it has uniformly involved the femoral or closely associated vessels in cases complicated by both endarteritis and endocarditis. Among these patients, therapy was supportive except in 3. Leaman[5] used chemotherapy and surgical removal of the fistula, as did Cutler and Wolf,[6] who gave a small amount of penicillin, but Heckler and Tikellis[7] recently reported a case in which massive dosages of penicillin were administered and the arteriovenous fistula was surgically excised. Nevertheless, this combined complication of an acquired arteriovenous fistula has proved uniformly fatal.

The purpose of this paper is to present an additional case of coexistent acquired and congenital arteriovenous fistulas with associated pseudoaneurysms complicated by endarteritis and endocarditis lenta due to *Str. faecalis*. Despite a most intensive antibiotic therapeutic regimen (Fig. 1), with coordinated surgical correction of the vascular defects, the patient died twenty months after the apparent onset of the septicemia. As far as can be determined from the available literature, this is the first case of this type in which the infecting organism has been *Str. faecalis*.

CASE REPORT

A 36-year-old Negro sergeant was in good health until August, 1950, when, in Korea, he incurred shell-fragment wounds of the chest and perforating and penetrating wounds of the right thigh involving the femoral vessels. He was hospitalized and treated without the development of any complication, but he left the hospital before completion of treatment to return to his unit in the combat zone. He later removed a bullet that was still present subcutaneously over the right femoral area. This self-inflicted wound became infected but eventually healed spontaneously. In December he noted a "buzzing" sensation in the region of the right femoral canal, with gradual development of a pulsating mass in that area. He was admitted to an Army hospital in Japan, where a diagnosis of arteriovenous fistula was made. On February 2, 1951, surgical correction was attempted. Two fistulas were found, one between the superficial femoral artery and vein and another between the profunda-femoris artery and vein. Although the transfer records were incomplete, our impression from the description of the operation report was that the superficial femoral vein was ligated and a plastic repair of the artery done, the vein being sacrificed but the femoral artery being preserved. The fistula of the profunda-femoris artery was repaired by excision of the fistulous tract, both artery and vein being preserved. The transfer records were incomplete regarding definite evidence of infection before operation.

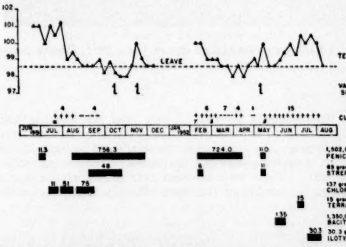

FIGURE 1. *Clinical Course during the Period June, 1951, to August, 1952, as Reflected by the Temperature Graph, with Indication of Dates of Surgical Procedures and a Résumé of Results of Blood Cultures.*

Summary of antibiotic therapy is indicated diagrammatically.

Penicillin therapy was begun postoperatively, but the patient continued to have systemic evidence of illness in addition to a swelling of the right leg. On May 21 he had a temperature of 105.4°F. *Plasmodium vivax* was discovered on blood smear. Physical examination revealed massive edema of the right leg and a pulsatile mass, with a machinery-like murmur, in the right femoral canal. The blood pressure was 122/58. Although he was treated adequately with chloroquine a low-grade fever persisted.

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He was evacuated to the United States, arriving at Walter Reed Army Hospital on June 26. Examination disclosed a low-grade fever and a blood pressure varying from 122/50 to 122/36. There was swelling of the entire right lower extremity, with evidence of a cellulitis over the femoral triangle. A pulsating aneurysmal mass with a thrill and bruit of systolic timing was present in the femoral triangle. In the lower thigh a continuous bruit could be heard in 2 areas, suggesting the possibility of multiple arteriovenous fistulas. There was no hepatosplenomegaly, petechiae or evidence of embolic phenomena. Although initially only a systolic apical murmur was heard on examination of the heart a blowing diastolic murmur of aortic regurgitation was later heard. There were no other cardiac abnormalities, and roentgenographic studies of the heart (Fig. 2), including cardiac fluoroscopy, revealed no definite abnormalities. The only significant laboratory data were a mild anemia (red-cell count of 3,900,000, hemoglobin of 10.5 gm. per 100 cc. and hematocrit of 34 per cent), a white-cell count of 9400, with 53 per cent neutrophils, a sedimentation rate of 30 mm. per hour and a negative serologic test for syphilis.

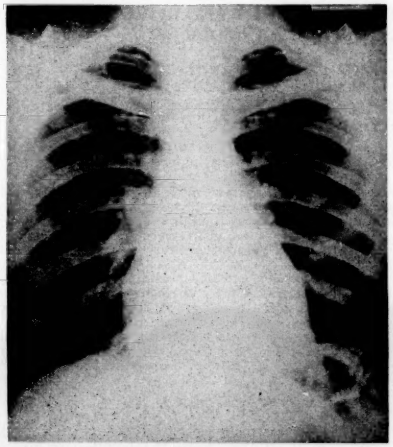

FIGURE 2. *Roentgenogram of the Chest in June, 1951, Demonstrating a Normal Cardiac Silhouette.*

The low-grade fever persisted. Because of a slight urethral discharge, mild urinary frequency with dysuria and urinary findings of pyuria, albuminuria and microscopic hematuria, a diagnosis of posterior urethritis was considered. An intensive course of penicillin therapy, followed by a course of chloramphenicol therapy, was initiated (Fig. 1). The genitourinary symptoms cleared, but the low-grade fever persisted. Blood cultures revealed a persistently positive culture of an alpha-hemolytic enterococcus that proved to be *Str. faecalis*. A suspected diagnosis of subacute bacterial endocarditis was thus confirmed. Sensitivity studies (Table 1) showed the infecting organism to be sensitive only to chloramphenicol. The effect of therapy with this drug is demonstrated in Figure 1. Repeat malaria smears revealed a recurrence of the plasmodia infection, and a course of chloroquine therapy was administered. In the following 4 months intensive antibiotic therapy was employed, penicillin and streptomycin being given (Fig. 1); chloramphenicol was discontinued because of a pustular erythema that was considered to be a toxic reaction. Benemid was added to the therapeutic regimen, and penicillin blood levels of 40 units per cubic centimeter were obtained. On this regimen the temperature became normal though blood cultures remained positive. On August 17 it was noted that the blowing diastolic murmur of aortic insufficiency had changed, becoming "cooing" in character, which suggested a probable perforation of the aortic valve. The patient was asymptomatic at this time, but otherwise the clinical picture was unchanged. Blood cultures became negative on August 27.

On October 12 the superficial arteriovenous fistulas of the lower thigh were removed surgically; they were considered to be of the congenital type. They showed no signs of being mycotic. Recovery was uneventful and the temperature remained normal. On November 16 a false aneurysm of the profunda-femoris artery was obliterated by ligation of the artery, but the false sac was not removed. After these surgical procedures the bruits and thrills previously present in the leg disappeared, and the swelling began to decrease.

The clinical findings were otherwise unchanged except for the development of early evidence of hypertrophy of the left ventricle on roentgenographic and electrocardiographic study. There was no evidence of congestive heart failure at this time. The patient became afebrile. It was decided that a bacterial cure had been obtained, and he was allowed to go on convalescent leave, with instructions to return if the symptoms recurred. He returned to the hospital on February 4, 1952, complaining of diarrhea, abdominal pain, nausea, vomiting and fever of several days' duration. Physical findings were unchanged from those observed before discharge. Cardiac murmurs revealed little alteration, and there was no evidence of an arteriovenous fistula. The swelling of the right leg had almost completely disappeared. Blood cultures were immediately drawn, and a nonhemolytic *Str. faecalis* was recovered. The change in hemolytic properties from the initial organism was considered to be a variant. Sensitivity studies (Table 1) showed the organism to be sensitive to chloramphenicol, but this was not given because of the previously demonstrated sensitivity reaction. It was decided to institute another course of penicillin and streptomycin therapy, but laboratory studies failed to reveal a synergistic effect. The abandonment of combined penicillin and streptomycin therapy on the basis of these laboratory data was a mistake. Penicillin dosage was gradually increased to 12,000,000 units daily, and with the aid of Benemid, blood levels of 40 to 80 units per cubic centimeter were obtained.

On February 18 definite evidence of left-sided cardiac failure became manifest by a diastolic gallop rhythm and pulsus

TABLE 1. *Tube-Sensitivity Studies and Hemolytic Reactions of Organisms.*

ANTIBIOTIC	ALPHA-HEMOLYTIC STREPTOCOCCUS	GAMMA-HEMOLYTIC STREPTOCOCCUS	BETA-HEMOLYTIC STREPTOCOCCUS		
	DEGREE OF SENSITIVITY ON JULY 24, 1951	DEGREE OF SENSITIVITY ON FEB. 11, 1952	DEGREE OF SENSITIVITY ON APR. 22, 1952	DEGREE OF SENSITIVITY ON JUNE 16, 1952	DEGREE OF SENSITIVITY ON JULY 22, 1952
	microgm./cc.	*microgm./cc.*	*microgm./cc.*	*microgm./cc.*	*microgm./cc.*
Chlortetracycline	40	50	20	40	—
Chloramphenicol	3	2	2	2	2
Oxytetracycline	50+	50+	49	50+	—
Penicillin	1*	5*	20*	10*	4*
Streptomycin	50+	50+	—	—	—
Erythromycin	—	—	—	—	0.4
Bacitracin	—	—	—	0.2*	0.2*

*Units per cubic centimeter.

alternans. An Austin-Flint murmur was audible at the cardiac apex, and cardiac size rapidly increased, indicating dilatation. Digitalization was instituted and maintained. On this regimen the patient remained asymptomatic, and by March 7 the low-grade fever had disappeared. At this time, however, blood cultures showed the enterococcus to have become beta hemolytic. Blood cultures became negative on March 12. The patient remained asymptomatic and afebrile though the "cooing" quality of the aortic diastolic murmur became more pronounced and the heart gave roentgenographic evidence of increasing dilatation. On April 22 penicillin therapy was discontinued because he absolutely refused any further parenteral medication. This was followed by prompt return of the enterococcus in the blood. When a transient episode of severe abdominal pain occurred, an embolization to one of the abdominal viscera was postulated although there was no objective evidence of embolization. A low-grade fever again appeared.

To remove a possible source of infection the thigh was again explored surgically on May 7, and a small, nonmycotic, false aneurysm of the lateral circumflex artery of the right thigh was excised. An episode of acute abdominal pain again occurred, and again the only explanation was that of possible embolization. Further evidence of cardiac failure became evident. Laboratory studies revealed the organism to be sensitive to bacitracin (Table 1). Therapy with this antibiotic extended over a 2-week period (Fig. 1) without significant nephrotoxic effect and with no effect on the deteriorating clinical course. Further therapy was then instituted with erythromycin* (Fig. 1) since sensitivity of the organism to this antibiotic was also demonstrated (Table 1). Dyspnea became pronounced. Pleural effusion developed, and on July 28 a thoracentesis removed 175 cc. of clear, amber fluid from the right side of the chest. Evidence of failure of the right ventricle became more prominent, with hepatomegaly, peripheral edema and marked venous distention. Roentgenographically cardiac dilatation was seen to increase rapidly. Blood cultures continued positive, and on August 2 the patient died suddenly without any specific premonitory signs or symptoms.

At post-mortem examination the body was that of a well developed and well nourished man. Scattered petechiae were present over the thorax. There was moderate acropachy. A well healed 21-cm. linear scar extended from the right inguinal region down the anterior aspect of the right thigh. There was moderate pitting edema of the right foot.

The peritoneal cavity contained 350 cc. of a slightly cloudy, dark-yellow fluid. When the thorax was opened 50 cc. of clear, amber fluid was found in the left pleural cavity and 250 cc. in the right pleural cavity. The pericardium contained 150 cc. of faintly cloudy, amber fluid. The heart was markedly dilated and hypertrophied, weighing 745 gm. The epicardial surface was smooth and glistening.

The right ventricle was dilated; its wall measured 5 mm. in thickness. The circumference of the tricuspid valve was 13 cm. The valve leaflets, chordae tendineae and papillary muscles were normal. The pulmonary valve measured 8 cm. in circumference. the valve cusps were normal. The left ventricle was markedly dilated, and its wall was 21 mm. thick. There was, in addition, a localized dilatation of the left ventricle just below the aortic valve, and loosely adherent to the endocardium of this region were numerous, friable, vegetative lesions varying in circumference from 1 to 5 mm. (Fig. 3). The aortic valve measured 7 cm. in circumference. The edges of the valve leaflets were firm, thickened and covered with numerous small, friable vegetations (Fig. 3). The posterior cusp contained a tear halfway through its midportion; the bodies of the other cusps were uninvolved. The inner aspects of the cusps appeared normal and the coronary ostia showed no abnormality. The aorta revealed no significant lesions. On the superior surface the mitral valve measured 12 cm. in circumference, there were several small hemorrhagic vegetations, and on the edges of the leaflets there were many small verrucae. A large vegetation was located at the base of the aortic cusp.

The right lung weighed 960 gm. Sections through the lower lobe revealed an embolus lodged in one of the larger vessels supplying this area, resulting in a wedge-shaped infarction. There was severe pulmonary congestion and edema. The left lung weighed 945 gm. and, except for the infarction, was similar to the right.

The spleen weighed 210 gm. and contained several areas of fibrous scarring believed to represent old infarcts.

*Kindly supplied by Eli Lilly and Company, Indianapolis, Indiana, in the form of Ilotycin.

The liver weighed 2340 gm. The external surface showed adhesions of the right lobe. There was a cross-shaped scarring extending deep into the liver tissue.

The right kidney weighed 270 gm. There were several umbilicated scarred areas over the surface to which the capsule was adherent. Scarring extended deeply into the renal tissue. The left kidney weighed 255 gm. and was similar in appearance to the right.

The brain, adrenal glands, gall bladder, pancreas, gastrointestinal tract and genitourinary tract were normal.

A linear incision was made along the length of the old, healed scar in the right femoral region. All the tissues in this area were markedly scarred and fibrotic, making dissection almost impossible. The femoral artery and vein were identified but could not be completely dissected. There was no evidence of aneurysm or arteriovenous fistula.

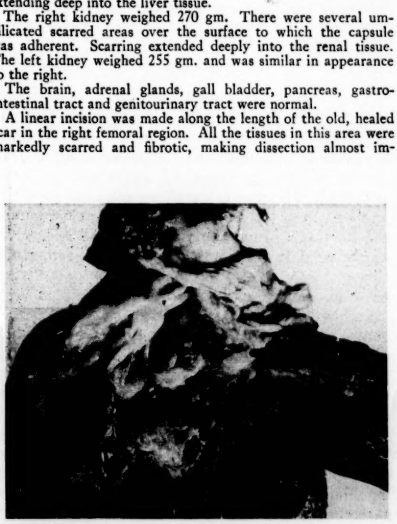

FIGURE 3. *Aortic Area Revealing Destructive and Vegetative Lesions of the Semilunar Valves, with Rupture of a Posterior Cusp. Note vegetative lesions on the endocardium and at the base of the aortic cusp of the mitral valve. A few small vegetations are present on the superior surface of this cusp.*

Microscopical examination of the heart revealed scattered foci of myocardial degeneration. Sections through the vegetations on the valve leaflets and endocardium demonstrated the typical picture of bacterial endocarditis. The valve leaflets were thickened and showed fibroblastic activity. The superficial vegetative lesions were composed principally of hyalinized fibrin in which numerous cocci were enmeshed. The myocardium immediately underlying these vegetations exhibited varying degrees of fibrotic degeneration.

The lungs disclosed moderate diffuse bronchopneumonia. Sections obtained from the area of infarction revealed the expected pathological features. The spleen was moderately fibrotic and congested with the residua of multiple small infarcts.

The most striking feature of the liver was severe centrilobular necrosis. The trabeculations and portal areas displayed considerable fibrosis, and bile-duct proliferation was a prominent feature. There was also a moderate infiltration of the portal triad areas by lymphocytes and occasional polymorphonuclear leukocytes.

The kidneys contained numerous infarcted areas within the renal parenchyma. These areas were markedly fibrotic, with accompanying degeneration of the glomeruli and tubules. The remainder of the renal tissue exhibited severe focal infiltration by lymphocytes. The glomeruli and afferent arterioles appeared normal except for an apparent, relative increase in the cellular elements of the glomeruli and minimal local thickening of the basement membrane. Many of the tubules were dilated and contained amorphous or granular casts and cellular débris. Some sections of the kidneys appeared normal.

The bone marrow demonstrated a moderate erythroid and myeloid hyperplasia. The lymph nodes, stomach, pancreas,

prostate, thyroid and adrenal glands and central nervous system disclosed no significant abnormalities.

Blood cultures from the aorta, left ventricle, pulmonary artery, liver, spleen and right femoral artery revealed a beta-hemolytic streptococcus of Lancefield Group D.

Discussion

The sequence of events that led to the development of the subacute bacterial endocarditis cannot be stated with absolute certainty. The patient, so far as could be determined, had no evidence of heart disease before the acquired arteriovenous fistula appeared. He was in excellent physical condition and had been the heavyweight boxing champion of the Far East Army Command. He had been given numerous physical examinations without demonstration of any cardiac abnormality. The past history gave no evidence of rheumatic fever or syphilis.

It has been suggested that an acquired arteriovenous fistula was present at the time of initial hospitalization and was not found because of the premature discharge of the patient from the hospital when he absented himself without leave to return to his unit. It is not definitely known when enterococcal septicemia first developed. It was probably incident to the known local infection that developed when he removed a bullet from the right inguinal region by means of a razor blade. Unfortunately, complete records of overseas hospitalizations have not been located. It is not known whether or not clinical evidence of infection was present when he returned to the hospital for treatment of the arteriovenous fistula. Likewise, pathological study of the resected fistula was not carried out. It is believed that endocarditis and endarteritis were already established at that time.

Although the development of bacterial endocarditis on a normal valve has been reported, it seems more reasonable to assume that the infection was secondary to an endarteritis of the acquired arteriovenous fistula. This has been the probable pathogenesis in all previously reported cases of coexistent arteriovenous fistula and endocarditis lenta. The exact cause of the valvular damage that occurs in the presence of an arteriovenous fistula, establishing a locus minoris resistentiae for the development of bacterial endocarditis, is not fully known. However, it appears to be related to cardiovascular stress. In this regard Lillehei and his associates[21, 22] have demonstrated the experimental production of endocarditis in dogs with arteriovenous fistulas, the lesions developing only if the arteriovenous fistula or fistulas were of sufficient size to cause a certain level of cardiovascular stress. It is interesting that the patient described above, as well as those in the other cases with this complication reported, had relatively large arteriovenous fistulas, involving the femoral vessels, and experienced prolonged latent periods before the development of endarteritis and endocarditis.

It is well known that enterococcal endocarditis is a formidable disease and at times refractory to all therapeutic efforts. With this fact in mind every therapeutic approach that has had reported success was attempted. The amount of antibiotic therapy given during the initial overseas treatment is unknown; varying amounts of penicillin were given before and after the initial operation. It is quite probable that these prophylactically administered and therapeutically inadequate amounts of antibiotic were a factor in further increasing the resistance of the enterococcus to these agents. One of the many difficulties encountered in the attempt to establish an adequate therapeutic regimen for this patient was the development of multiple variants by the infecting enterococcus. The variations were unique in both enzymatic activity and biochemical reactions (Table 1). A discussion of these variations is beyond the scope of this report; the cause of these variations is still a subject of controversy. The problems encountered with this organism will be more fuliy explored in a separate article.[23]

The occurrence of cardiac failure during the course of subacute bacterial endocarditis is indicative of a grave prognosis. Therefore, it must be pointed out in all fairness that bacitracin was employed after the development of congestive heart failure when the disease had progressed to a point where recovery was improbable. Certainly, the utilization of erythromycin terminally cannot be taken as an adequate therapeutic trial of the antibiotic.

It should be emphasized that the presence of an arteriovenous fistula should always alert one to the possibility of a complicating endarteritis or endocarditis or both, if there is even the slightest evidence of infection. Although all previously reported cases of this unwelcome complication have been unsuccessfully treated, there is no reason why immediate surgical correction of the vascular defect, combined with the effective antibiotic therapy now at hand, should not offer hope of recovery. In the case presented above, the failure of early recognition was probably one of the main factors in the refractory course of the disease. However, additional factors were the resistance of the enterococcus to antibiotic therapy and its versatility in adapting itself to this therapy by multiple variations. As emphasized by James[24] this occurrence of alpha-hemolytic, beta-hemolytic and gamma-hemolytic properties of the enterococcus should be recognized. The identification of an alpha-hemolytic streptococcus should always be pursued to its completion so that an enterococcus will not be overlooked in the establishment of an early effective treatment of the infection.

Summary

A case of subacute bacterial endocarditis due to *Streptococcus faecalis* is presented. This occurred as a complication of traumatic arteriovenous fistulas and subsequent endarteritis.

Surgical correction of the fistulas and intensive antibiotic therapy were unsuccessful.

The pathogenesis of the development of an enterococcal endocarditis on a previously normal aortic and mitral valve in the presence of an acquired arteriovenous fistula is discussed.

Many physicians of the armed forces contributed to the care of this patient through his prolonged hospitalization. Only through their efforts and medical observations were the details of this report made possible.

We are indebted to Lieutenant Colonel Ervin Ginzberg, instructor in the Surgical Department, Medical Military Academy, Belgrade, Yugoslavia, for his assistance in the translation of foreign articles.

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INFANTILE CORTICAL HYPEROSTOSIS*
An Inquiry into the Etiology and Pathogenesis

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THE syndrome that has become known as infantile cortical hyperostosis, after the suggestion of Caffey and Silverman,[1] is characterized by the usually sudden onset of swelling of the face, thorax or extremities, hyperirritability, fever, fluctuating course and roentgenographic evidence of periosteal new-bone formation. Probably the first case was described by Roske,[2] but the syndrome was not appreciated until the publication of the descriptions of the clinical and roentgenologic picture.[1, 3, 4] There are now over 60 cases in the literature. Sherman and Hellyer[5] reviewed their x-ray films taken of infants during the preceding twenty years and found no case of infantile cortical hyperostosis, suggesting either that this syndrome is new or that the incidence has rapidly increased in recent years.

Infantile cortical hyperostosis has been encountered in all parts of the world, in almost all ethnic groups[2, 5-13] and without regard to social level. Of the 69 cases analyzed[1-12, 14-38] (including our 10 cases and excluding 12 of Caffey's[39] cases not individually reported) 37 occurred in male and 32 in female patients. Age seems to be a decisive factor; indeed, Caffey[39] regards an onset later than five months of age as a cause for questioning the diagnosis. The average age at onset in the cases tabulated was nine weeks, the range being five weeks before to five months after birth.

The search for the etiology of this syndrome has been unrewarding. Infection was logically considered first because of the findings of anemia, leukocytosis, elevated erythrocyte sedimentation rate, fever and a remitting course. As in many of the reported cases several of our patients had intercurrent bacterial infections, usually respiratory. Bacteriologic and viral investigations have been repeatedly negative.[6, 11, 33] There has been no evidence that trauma, allergy or endocrinopathy is an

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etiologic factor. Caffey has commented on the fact that these infants are frequently born to mothers thirty years of age or older. The mothers of 4 of 8 of our group were over thirty at the time of birth of the infant. In one case the mother was seventeen years old at the time of birth of her child, who subsequently manifested infantile cortical hyperostosis. This is reminiscent of the pattern seen in mongolism, which Benda[40] attributes to a "threshold condition of hormonal sterility." The incidence of reported miscarriages in the mothers of patients described in the literature is lower than that normally expected; however, that found in our group conforms with the expected incidence.[41] The syndrome has been described in infants born prematurely and those delivered by cesarean section,[1, 5, 9, 19] but there is no evidence that would incriminate these factors etiologically. In most cases the birth has been normal.

We believe the syndrome to be more frequent than is commonly considered. The patients in the following 10 cases were seen in the private pediatric practice of one of us (J. B. S.) over a four-year period.

Case Reports

Case 1. E. M. G. had swelling and tenderness of the right leg, first noted when 8 days of age, followed by swelling and tenderness of the left forearm when she was 12 days old. Hyperirritability was noted from the onset. She was admitted to the Babies Hospital when she was 1 month of age. She had developed normally and evidenced no constitutional reaction except irritability. She had tenderness and swelling of the right leg, left forearm and mandible. There was pseudoparalysis of the involved extremities.

Figure 1. *Roentgenogram of the Forearm in Case 1, Showing Marked Involvement of the Radius and Moderate Involvement of the Ulna at Six Weeks of Age.*

The father was born in the Dutch East Indies of Dutch parents and had had tertian malaria, treated with quinacrine hydrochloride 18 months before the birth of this child. The mother had had "kidney trouble" before this pregnancy and hyperemesis during the first 5 months of pregnancy; she had gained 20 pounds in weight during the last 4 months.

The infant had a moderate anemia and leukocytosis. Culture of material aspirated from the tibia was sterile.

The initial roentgenograms showed changes characteristic of infantile cortical hyperostosis involving the mandible, right tibia and fibula, left ulna and radius (Fig. 1). At 7 weeks of age there was progression of the old lesions, and involvement of the clavicles, right scapula and a rib was demonstrated. Films obtained at 3½ months of age revealed improvement of the previously noted lesions. Films taken in May, 1952, disclosed a residual bowing deformity of the right tibia and fibula and left radius.

Figure 2. *Roentgenogram of the Right Leg in Case 1 at Sixteen Months of Age, Showing the Anterior Bowing of the Tibia, a Residuum Frequently Seen after Extensive Involvement.*

The hospital course was benign; there was only a single rise of temperature. Clinically, all symptoms resolved at 9 months of age. However, films taken when the child was 3½ years of age showed residual deformity of right tibia and left radius (Fig. 2).

Case 2. P. C. G. (sister of the patient in Case 1) was first seen at 6 months of age on August 8, 1953. At birth a swelling of the right arm, which was slightly tender, was noted. A roentgenographic survey showed involvement of both clavicles and marked proliferation of periosteal new bone along the diaphysis of the right radius. The involvement of the radius was apparently of several weeks' duration since the proliferative process was extensive and bowing had already occurred. When the patient was 2 months of age slight swelling and tenderness of the left leg were noted. At 6 months of age there was some swelling of the left leg and a mild gross deformity of the right

forearm. A roentgenologic survey at this time revealed involvement of the mandible, left clavicle, right femur and left tibia. There was a residual bowing of the right radius.

CASE 3. J. A. W., a Cherokee Indian female infant, suddenly manifested a painful swelling of the left lower leg when she was 2 weeks old. No fever was noted. The infant was breast fed for the first 3 weeks.

There were 10 normal siblings; another had died at birth. The parents were middle-aged.

A moderate anemia and leukocytosis were found. X-ray examination taken when the patient was 3 months old disclosed involvement of the left tibia and fibula.

The course was benign, and all swelling had subsided when she was seen at 6 months of age. No further symptoms had evolved.

CASE 4. E. B. became irritable, anorexic and restless during sleep, and cried out when handled when he was 3 months old. In the following week mumps was noticed. The painful mandibular swelling subsided and recurred. On admission, at 4 months of age, the right leg was also observed to be swollen and tender, and he had a conjunctivitis associated with an upper respiratory infection.

The mother was 21, and the father 23. The mother had had eclampsia before delivery.

A moderate anemia and leukocytosis were found. X-ray examination revealed the changes of infantile cortical hyperostosis involving the mandible, right tibia and left femur. Roentgenograms taken at 7 months of age showed little change. Films obtained 4 months later demonstrated a slight increase in the diameter of the right tibia.

The patient was clinically well at that time; there has been no recurrence, and no residua have been observed.

CASE 5. R. R. O. began to be irritable intermittently when he was 11 months old. Swelling of the mandible appeared suddenly 1 week before admission to the Babies Hospital when he was 4 months old. He became febrile and anorexic. He was thought to have mumps. A tender swelling over the medial portion of the left clavicle was noted.

There were 2 normal siblings and a history of 1 miscarriage. The father was 41, and the mother 34 years old. There was a family history of acute rheumatic fever, rheumatoid arthritis, Bright's disease, hay fever and asthma, diabetes mellitus and organic epilepsy.

There was no anemia and only a slight leukocytosis and elevation of the erythrocyte sedimentation rate. Roentgenograms demonstrated bilateral involvement of the mandible, but no lesion of the clavicle could be discerned. Films obtained 2 months later showed progression of the mandibular lesions; clavicular involvement was then demonstrated. Roentgenograms were normal at 17 months of age.

In the hospital the patient ran a persistent fever. The clinical symptoms cleared before he was 17 months old.

CASE 6. R. B. P. became feverish and hyperirritable at 6 weeks of age, and because of a tendency to retract his head and a high-pitched cry he was suspected of having meningitis. When seen at 2 months of age, he had swelling and tenderness of the mandible.

The mother was 17, and the father 23 years of age.

A mild anemia and leukocytosis were present. A roentgenographic survey of the skeleton revealed changes consistent with infantile cortical hyperostosis involving the mandible and right clavicle.

The patient was febrile during the 7 days of observation. X-ray films taken at 3 months of age disclosed a mild periosteal reaction of the left tibia and progression of the process in the mandible and right clavicle. Examination at 14 months of age showed complete resolution, but the mandible was more radiopaque than normal. All swelling cleared when he was 19 months old, and at 2 years of age he was well and without evidence of residua. (No abnormalities were apparent in a sibling 8 months of age.)

CASE 7. T. S. began to have fever and irritability at 3 months of age; mandibular swelling was observed when he was 13 weeks old. He was pale and had an upper respiratory infection at the time of admission.

The parents were 34 years of age. There were 5 siblings, 1 of whom had had an attack of acute rheumatic fever.

There was no anemia, but a moderate leukocytosis was found. X-ray studies on admission showed only mandibular involvement.

The temperature was 102.4°F. on admission. On October 21, 1951, there was marked involvement of the mandible, and the left clavicle demonstrated some involvement. Clinically, all swelling had subsided at 6 months, and at 2 years of age the patient was in good health without recurrence or residua.

CASE 8. E. E. C., when she was 2 months of age, had a sudden onset of swelling of the lower portion of the face, pseudoparalysis of the right leg, fever, but no increase in irritability. At the age of 6 months there was no clinical swelling, but she protected her right leg. Roentgenograms taken at this time showed periosteal elevation and thickening of the mandible and the length of the shafts of the right tibia and fibula. The left scapula was also involved.

Clinically, all symptoms had cleared by the 8th month. At 13 months of age she was healthy, and roentgenograms were normal.

CASE 9. D. H. had the sudden onset of fever and irritability when she was 2 months old. At 7 weeks of age she was found to have fever, irritability, swelling and tenderness of the mandible, moniliasis and a purulent otitis media.

The laboratory reported a moderate anemia and leukocytosis. X-ray studies revealed periosteal new-bone formation of the mandible only.

The swelling of the mandible had subsided at 6 months of age. Six months later there had been no recurrence.

CASE 10. Since birth C. W. had fretted when she was handled. A tender swelling of the left side of the face was noted at 5 weeks of age. She was moderately pale.

The mother had had a tubal pregnancy 11 years previously. The maternal grandmother had diabetes mellitus.

A moderate anemia and slight leukocytosis were present. Roentgenograms showed periosteal new-bone formation of the left side of the mandible. At 8 weeks of age, the right side of the face became swollen for 3 days. Subsequently, x-ray examination demonstrated involvement of the mandible on the right side. The tenderness had subsided and no further lesions were found on x-ray study at 7 months of age.

Unless noted, the family history, mother's antenatal history, birth history and feeding history, including proper dosage of supplementary vitamins, were normal. The patient was the only child unless otherwise noted. Treatment was symptomatic; antibiotics did not alter the course of the disease, but they were of value for intercurrent infections. All patients have either been seen recently or reached by mail for follow-up report and closer scrutiny of possible abnormalities during the antenatal period, but nothing seemingly pertinent or consistent has been discerned. Serum calcium and inorganic phosphorus determinations were obtained on half the patients and found to be normal, but the serum concentrations of alkaline phosphatase and vitamin C and D were not obtainable. Serologic tests for syphilis, skin tests for tuberculosis and urinalyses were uniformly negative. Biopsies were not obtained.

DISCUSSION

Since the evidence of infection, trauma, allergy, endocrinopathy, maternal causes, birth factors or dietary aberrations as possible etiologic agents is slight, other avenues of approach have been investigated. There is increasing evidence that the fault may lie in some intra-uterine or genetic factors. Associated congenital anomalies were reported in 2 cases,[3, 19] and in the siblings of another case[4];

however, none were observed in our group. A higher incidence of associated anomalies might be expected if intra-uterine factors were responsible. The suggestion was made by Barba and Freriks[20] that the condition represents embryonal osteodysgenesis consequent to a local defect in the vascular supply resulting from rapid growth, preliminary ossification, muscle pull and change in relations that lead to a certain amount of distortion of bone. Racely et al.[32] suggested that the primary pathological process was in the periosteum.

The occurrence of cases in siblings gives weight to the suggestion that genetic factors are fundamental. Van Zeben[8] reported 3 cases, 2 in siblings of whom the third was a second cousin. Cases 1 and 2 reported above were siblings. Barba and Freriks[20] described the disease in siblings; the diagnoses in both were made antenatally by x-ray examination of the mother. Boyes and Demy[22] reported the occurrence in siblings; however, in their first case the first lesion developed at ten and a half months of age. Kitchin[21] presented a case of infantile cortical hyperostosis in a patient whose mother appeared to have had the syndrome in infancy. In the light of these cases it became difficult not to give serious consideration to a genetic etiology. The familial pattern seen in these infants and the fact that the manifestations have been shown to be present in some cases antenatally and that the average age of nine weeks at onset is similar to that in pyloric stenosis (which has been suggested as an inherited abnormality[42-44]) indicate that this entity is also an inherited trait, the evidence being insufficient for exact definition of the *modus operandi*. It is of interest that the case reported by Jenkins and Scott[12] was associated with pyloric stenosis.

The discrepancies in the descriptions of the pathology of infantile cortical hyperostosis result from the paucity of autopsies, the dearth of adequate specimens when biopsies were obtained and the virtual absence of biopsy material from the lesions in the earliest phases of the process. A synthesis of the pathology from the reported biopsies[1, 2, 4-6, 8, 19, 26-27] and autopsies[23, 24] would indicate that the periosteum is mucinous and thickened but is stripped easily from a thickened bone of irregular contour. Microscopical examination demonstrated involvement by the pathologic process of the overlying soft tissues as well as the bone and periosteum. Fibrous strands were found to extend from the periosteum into the overlying fascia, muscle and adipose tissue. Evidence of degeneration of the soft tissues over the areas of bone involvement was observed. The arteries of the overlying soft tissues and periosteum showed intimal proliferation. The periosteum was hyperplastic and edematous. In the areas of osseous involvement the haversian pattern was imperfect and the haversian spaces were lined with osteoblasts and contained poorly vascularized, loose fibrillary tissue. Never was there evidence of hemorrhage or inflammation.

It seems reasonable that the arterial lesions are primary, as suggested by Barba and Freriks.[20] The resultant local hypoxia produces edema and hyperplasia of the periosteum, which in turn results in the overproduction of imperfect bone. Whereas hyperemia causes resorption of bone, diminution of the blood supply stimulates new-bone production.[44] The lesions are tender and painful when the proliferative process causes tension of the periosteum. The fever, the leukocytosis and the elevation of the erythrocyte sedimentation rate are due in part to the tissue necrosis. Anemia and lowering of the serum iron is a nonspecific response to a persistent fever from any cause. Augmentation of the metabolic rate in a patient with limited iron stores and decreased iron absorption consequent to fever are ancillary factors in the production of the anemia. The *vis a tergo*, the arterial intimal proliferation, we hold to be an inherited defect.

This syndrome invariably begins in the first five months of life. The average age at onset in the cases reported above and those collected from the literature was nine weeks; 2 cases were diagnosed in utero.[20] The abnormality in Kitchin's[21] case was noted six hours after birth, and in our Case 2 at birth. The onset is usually sudden in an infant previously apparently well whose nutritional status is characteristically good. There is no set order of appearance of the symptoms of the triad of fever, irritability and swelling over bone. In 7 of our 10 cases the fever and irritability preceded the clinical evidence of bone involvement. Cases 2 and 3 had no known fever, and Caffey[38] mentioned such a case, which was observed closely without an elevation of temperature. Cases 2 and 8 showed no irritability. Variation in the clinical and x-ray pattern of bone manifestations is mentioned below. Generally speaking, the degree of febrile response and irritability correlated with the extent of bone involvement. Pallor was a common finding. Antecedent or intercurrent infections, usually upper respiratory, have been noted in many cases, including two cases that followed vaccination[28, 29]; however, in most cases no infection was present.

Our cases showed a striking uniformity of physical characteristics of the tumors that was consistent with the description of other cases. There was no erythema or increased warmth of the overlying skin (which may be blanched and tense, however, if the new-bone formation beneath is extensive). The soft tissues were movable over the tumors, which were deep, firm and usually tender. Motion of the involved part was often limited by pain, and typical pseudoparalysis was seen in Cases 1 and 8. Rib involvement may cause a pleuritic reaction. The size of the swelling varied markedly as the disease progressed through exacerbations and remissions. In an individual case, as was demon-

strated in our group of cases, only one or several bones may become involved. Cases 1 and 2 had residual osseous deformity. In these cases, as in those described by others,[1, 8, 21, 30-32] residual osseous deformity followed extensive involvement.

In 8 of our cases, followed long enough for healing to be evaluated, the average age before clearing of all clinical signs and symptoms was nine and a half months; for resolution of the x-ray evidence of disease in 4 cases, twenty-seven months was required. The averages for the cases in the literature are approximately the same. The occurrence of residual deformity of the involved bones in some cases has been noted. The prognosis for life is excellent, but this syndrome is not so benign as it was formerly believed to be. There are 4 recorded deaths: 3 were due to infection[8, 23, 32]; in the other, the cause was not known. Three patients in unreported cases have died; in one of these the primary cause, apparently, was infantile cortical hyperostosis.[45]

In the majority of these infants an anemia and leukocytosis develop at some time in the course of the illness. An elevated sedimentation rate and serum alkaline phosphatase are frequently seen. Pertinent negative data include the serologic test for syphilis, tuberculin skin test, bacterial and fungous skin tests, urinalysis, determinations of serum calcium and inorganic phosphorus, and serum vitamin A and C concentrations. Cerebrospinal fluid has been examined in several cases and found to be normal.

The diagnosis can be strongly suspected clinically, but definitive diagnosis is dependent on the roentgenologic findings.[46] The basic lesion is subperiosteal new-bone formation along the diaphysis of the bone. There is no roentgenographic evidence of involvement of the metaphysis or the epiphyseal centers of ossification. The early lesions may not be seen on the x-ray films or may be evidenced by a narrow margin of increased density beneath the periosteum that later thickens and becomes an obvious lesion characteristic of infantile cortical hyperostosis with obvious elevation of the periosteum and piled up periosteal new bone. In the later stages of the disease the originally thickened bone may heal, with resorption from within, leaving an enlarged bone, with a thin cortex and an enlarged medullary cavity.[38] Dentition has not been reported to be affected.

Practically all bones have been reported involved except the vertebras. Involvement is usually asymmetrical. Tabulation of 69 cases from the literature and our own cases revealed the following incidence of involvement of the stated bones: mandible, 77 per cent; tibia, 44 per cent; ulna, 36 per cent; clavicle, 35 per cent; ribs, 32 per cent; humerus, 32 per cent; femur, 32 per cent; fibula, 18 per cent; pelvis, 6 per cent,[30, 32, 38, 37]; and skull, 3 per cent.[5, 34] These percentages are only an indication. Metatarsal involvement has been reported,[28] and involvement of the phalanges of the hand has been seen.[13] Probably, other bones were involved in some of these cases but overlooked because complete roentgenographic surveys were not made in all cases. It is also possible that lesions developed and subsided in the interval between x-ray examinations.

The presenting symptoms or findings may suggest one of a number of different possibilities, such as parotitis, syphilis, scurvy, rickets, osteomyelitis, tuberculosis, poliomyelitis, meningitis, acute rheumatic fever, trauma (ossifying subperiosteal hematoma), nonspecific periosteal reactions, osseous cancer, leukemia, poisoning, vitamin A intoxication, allergy, erythroblastic anemia and Engelman's disease. In most cases the differential diagnosis can be made easily and quickly.

The best treatment is symptomatic and supportive. Sedation is frequently indicated for the hyperirritability. An adequate diet with supplementary vitamins and transfusions for anemia are helpful supportive measures. Hormonal therapy (ACTH and cortisone) has been tried in 12 cases[20, 36, 46] and appears to have shortened the course of illness. Until recently it was believed that hormone therapy should be reserved for severe cases that could not be controlled by other measures, in view of the dangers involved in such therapy in young infants. The occurrence of a mortality from the disease and the suggestion that cortisone might prevent the deformities in the severe cases[47] indicate that a less stringent attitude should be adopted toward the carefully controlled use of cortisone in infantile cortical hyperostosis.

Summary and Conclusions

Infantile cortical hyperostosis is the clinical manifestation of an inherited defect of the arterioles supplying the affected areas. The resulting hypoxia causes focal necrosis of the over-lying soft tissues and proliferative reaction of the periosteum.

A brief description of the clinical manifestations, roentgenologic findings, prognosis and treatment, with a review of the literature, is presented.

A report of 10 cases from a private pediatric practice is added to the literature with the comment that the syndrome is more common than is generally appreciated.

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ANGIOMATOSIS RETINAE*

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A UNIQUE feature of military medicine is the opportunity it provides for periodic physical examination of young adults. These examinations offer an unparalleled situation for the diagnosis of asymptomatic disease in this generally healthy group. Detection of retinal abnormalities on routine examination of the ocular fundi led to the diagnosis of the case of angiomatosis retinae reported below.

Angiomatosis retinae (von Hippel's disease) is a comparatively rare disease characterized by the presence of one or more hemangioblastomas of the retina and the destructive changes secondary to these tumors. It was first described in 1879 by Panas and Remy[1] and thereafter by several authors under a variety of titles until 1904, when von Hippel[2] established angiomatosis retinae as a clinical entity. However, the relation between this retinal disease and systemic disturbances, particularly cystic hemangioblastomas of the central nervous system, was not fully appreciated until the monumental work of Lindau[3] was published in 1926. After the pathologic process had been defined the number of observations increased rapidly, and in 1943 Cordes and Dickson[4] noted approximately 160 cases cited in the literature.

Angiomatosis retinae typically appears in young adults and is most commonly noted in the third decade of life,[5] though it has been detected in a fetus[6] and in a fifty-year-old woman.[7] Males are affected more frequently than females in the ratio of 62:38.[8] Either eye may be involved, and in 50 per cent of the cases the process is bilateral.[7, 9]

The influence of heredity is definite, and a familial factor can be demonstrated in 20 per cent of the cases.[10] When such a factor is present, the disease is usually transmitted as an irregular mendelian dominant without evidence of sex linkage.[11, 12]

Diagnosis of this disease may be difficult because the disorder is slowly progressive and appearance of the fundus varies greatly at different stages of clinical evolution. Perhaps the earliest demonstrable alteration in the fundus is fullness of a retinal vein, proceeding to immense dilatation of this vein and its parallel coursing branch of the central retinal artery. These vessels may demonstrate a wide

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variety of physical signs, and common findings are marked tortuosity, loops and kinks, in addition to variations in caliber noted typically as beading or segmentation of the arterial branch.[5]

These engorged vessels extend for a variable distance from the optic disk and, usually in the extreme temporal periphery of the fundus, terminate in a fan-shaped anastomosis between the two vessels.[13] From this area of anastomosis the characteristic neoplastic lesion of angiomatosis retinae develops. This lesion is a round or oval, sharply outlined, globular mass that is cherry red to pale pink. The tumors vary in dimension, — up to several disk diameters in extent, — and as many as three separate tumors have been present in a single eye.[2, 13]

As the pathologic evolution continues, tiny yellowish flecks of exudate appear near the tumor, along the course of the feeding vessels, in the macular area and near the disk.[7] Occurrence of exudative changes at a distance from the angiomatous lesion attests to the wide extent of the ocular disturbance and leads to the formation of confluent sheets of subretinal exudate. Hemorrhages into the retina or vitreous may occur during the development of these vascular and exudative alterations but, generally, do not constitute a major feature of the disease.

Retinal detachment may precede the exudative changes, occur simultaneously with them or develop at a later stage. Initially, detachment appears as a small area in the periphery or as one or more bullous elevations,[5] but eventually the retina becomes completely detached.[14]

The final stages of the process are dominated by an iridocyclitis, complicated cataract and a painful secondary glaucoma leading to further destruction and terminating in phthisis bulbi.

Although hemangioblastoma of the retina does not metastasize, treatment is definitely indicated in view of the loss of vision and destruction of the globe resulting from progressive disease. The need for effective therapy is emphasized by the high incidence of binocular involvement with its attendant blindness. However, all authors agree that treatment is difficult and success possible only when the tumor can be destroyed or arrested in its early stages. The two principal types of treatment are irradiation and electrosurgery.

Irradiation has been employed with radium,[16] radon seeds[16] and x-ray therapy.[17] Cordes and Schwartz[18] recently presented an eleven-year follow-up study of a patient given x-ray treatment. Vision in one eye was 20/20 although a new retinal hemangioblastoma had become evident despite treatment with a total of 3800r.

The first successful treatment with electrosurgery was reported in 1939 by Weve,[19] and there have been several subsequent reports of satisfactory therapy with diathermy.[20-23] The obvious advantage of electrosurgery is that the coagulating effect can be intense and yet sharply restricted to the tumor area. Thus, the general exposure necessitated by x-ray therapy is avoided. Consequently, it is the general opinion that electrocoagulation is the treatment of choice in most early cases of angiomatosis retinae in which the lesion is a single, localized neoplasm and that x-ray therapy is indicated when diffuse, extensive, multiple lesions are present.[22, 24, 25]

In summary, it may be stated that angiomatosis retinae is a comparatively rare hereditary disease most commonly affecting young adult males. The disease is clinically characterized by greatly dilated retinal vessels serving one or more globular, pink tumors usually located in the periphery of the retina. Growth of the tumor is associated with sheets of subretinal exudate and retinal detachment terminating in a destructive iridocyclitis complicated by a secondary glaucoma. Therapy must be undertaken early in the course of the disease, and electrocoagulation of the tumor is usually the treatment of choice.

Case Report

A 29-year-old single man was admitted to the hospital on May 19, 1953, because routine physical examination disclosed abnormally large retinal vessels. There was no history of ocular infection, operation or serious eye injury. Detailed review of ocular symptomatology was negative though the patient had worn corrective lenses intermittently since 1947.

The past history was negative for significant systemic disease, and a general review of symptoms was noncontributory.

The family history revealed that both parents were living and well and that 3 sisters, aged 22, 20 and 18, were in good health. There was no history of hereditary disease.

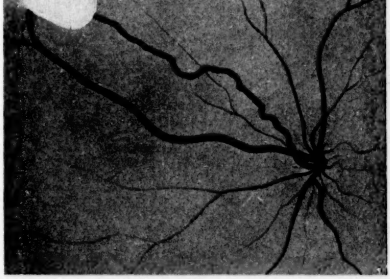

Figure 1. *Appearance of the Left Ocular Fundus before Operation.*

A greatly enlarged, tortuous and beaded retinal artery extends from the optic disk in a superior and nasal direction to an oval, globular, reddish-pink hemangioblastoma. Accompanying the retinal artery is an immensely enlarged retinal vein. The remaining retinal vessels and optic disk are normal, and no hemorrhages or exudates are present.

Physical examination was negative except for the ocular findings. Eye examination disclosed a visual acuity of 20/20, Jaeger 1, in the right eye and 20/40, Jaeger 1, in the left eye. Visual acuity in each eye was 20/20, with the following refractive correction: right eye, + 0.25 — 0.25 x 30; and left eye, + 0.25 — 1.50 x 160. Ocular adnexa and motility were within normal limits, and ocular tension was 19 mm. of mercury (Schiøtz) in each eye. The pupils were round, regular and equal, with physiological reactions to light and accommodation.

The right eye was normal in all respects.

The left eye showed no deviation from the normal except for the examination of the ocular fundus (Fig. 1), which revealed a greatly enlarged, tortuous and beaded retinal artery extending from the optic disk in a superior and nasal direction. This vessel passed to a discrete, oval, globular, reddish-pink hemangioblastoma measuring 2 disk diameters in greatest dimension. Accompanying the retinal artery was an immensely enlarged retinal vein, which was uniform in caliber and traveled from the tumor to the disk in a more direct line than the artery. The vessels could not be traced beyond their entrance to the tumor mass. Pressure on the globe caused pulsation in the veins and arteries but not in the neoplasm. The optic disk and remaining retinal vessels were not abnormal. There were no hemorrhages or exudates, and no area of retinal detachment was present.

The retinal tumor was localized with the hand perimeter in a meridian 30° above the horizontal and 55 to 60° nasal to the fixation point. Visual-field studies were normal except for an absolute negative scotoma 10° in diameter located in the inferior temporal field 30° below the horizontal and 60 to 70° from the fixation point.

Neurologic and neurosurgical consultations disclosed no stigmas of intracranial or spinal-cord dysfunction. Special studies such as ventriculograms and angiograms were not advised.

Routine laboratory work was within normal limits, and x-ray examination of the skull and cervical spine was indeterminate.

On May 27 diathermy coagulation of the retinal tumor was performed. After routine preparation and local anesthesia with 0.5 per cent tetracaine (Pontocaine) hydrochloride and 2 per cent lidocaine (Xylocaine) hydrochloride, the conjunctiva medial and superior to the limbus was incised, and the medial rectus muscle was isolated, secured with No. 000000 catgut sutures and divided at its insertion. The point on the scleral surface corresponding to the neoplasm was localized, and a Walker pin inserted. With this aid to localization 10 to 15 applications of the diathermy needle were made to the tumor and the area immediately surrounding the lesion. The medial rectus muscle was then fixed to its scleral insertion, and the conjunctiva was sutured in routine fashion.

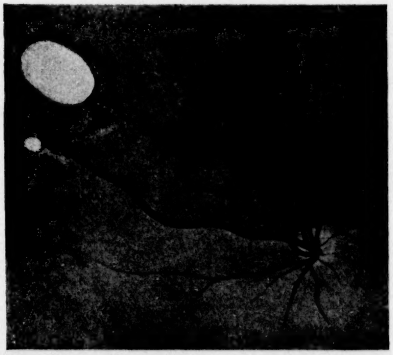

FIGURE 2. *Appearance of the Tumor Approximately Three Months after Diathermy Coagulation.*

The mass is essentially unchanged in size though whiter and less active in appearance. Surrounding the neoplasm is a ring of pigmented chorioretinitic scars, and the retinal artery and vein supplying the lesion are decreased in caliber. There are no hemorrhages, exudates or indications of retinal detachment.

The patient had an uneventful postoperative course, and visual acuity remained 20/20 with corrective lenses. Periodic follow-up examinations showed the tumor to be essentially unchanged in size though whiter and less active in appearance. The neoplasm was surrounded by a ring of pigmented, chorioretinitic scars. Several of these scars were across the path of the feeding vessels. The retinal artery and vein supplying the tumor were decreased in caliber though tortuosity and beading of the artery persisted.

Examination on August 25, approximately 3 months after operation, disclosed no progression of the treated neoplasm (Fig. 2). The lesion still appeared whiter than preoperatively, and there were no exudates, hemorrhages or indications of retinal detachment. Examination of both eyes revealed no additional neoplastic changes, and the visual acuity in each eye was 20/20 with refractive correction.

DISCUSSION

To appreciate variations in clinical evolution and to apply therapy intelligently, understanding of the fundamental pathology of angiomatosis retinae is essential. The basic lesion is the hemangioblastoma, which has been classified by Cushing and Bailey[26] as a true vascular tumor of mesodermal origin capable of slow, progressive growth though lacking the ability to metastasize.

The primary microscopical characteristic of these angioblastic tumors is the presence of primitive endothelial cells known as hemangioblasts. These pleomorphic cells may be present as solid clusters, or they may appear as endothelial elements lining vascular channels, and they are capable of forming a reticulum. By phagocytosing fat and lipid, hemangioblasts may develop the foamy cytoplasm of fat-granule cells and are then known as pseudoxanthoma cells.[9]

Another feature of these tumors is the glial proliferation incited by the hemangioblasts. This glial reaction in and surrounding the tumor may be extensive, but its purely secondary nature has been emphasized by its lack of pattern[25] and the observation of an early tumor devoid of glia.[27]

Cysts in the neoplasm and adjacent retina were noted in even the earliest histologic studies and are usually a prominent finding. These cysts are the result of vascular changes that induce transudation of blood plasma, and they are significantly related to retinal degeneration and eventual retinal detachment.

Grossly, the tumor develops as a sharply delineated nodule in the fibrovascular layer of the retina. As the lesion expands it may invade the choroid[28] but usually extends into the vitreous. Collins[29] reported a case in which the hemangioblastoma was aggressive enough to encroach on the cornea, and perforation of the globe has been reported.[30]

The basic pathology of hemangioblastomas is not confined to the eye, and the responsibility of the physician does not end with the diagnosis and treatment of retinal angioblastic tumors. The association of these retinal neoplasms with central-nervous-system hemangioblastomas and malforma-

tions of somatic organs has been generally recognized since Lindau's reports. In at least 25 per cent of all cases of angiomatosis retinae signs of central-nervous-system involvement develop,[10] though these signs may occur ten[4, 7] to fourteen years[22] after detection of the retinal lesion.

The most common central-nervous-system lesion in Lindau's familial syndrome is the cystic angioblastic tumor of the cerebellum. These tumors are indistinguishable clinically from other new growths in the cerebellum, but cerebellar angioblastic cysts are usually associated with a long history of intermittent headache of the hydrocephalic type, combined with the relatively late onset of papilledema and delayed signs and symptoms of cerebellar dysfunction.[17, 31] Less common sites for angioblastic neoplasms of Lindau's disease are the spinal cord, medulla, pons and rarely the cerebrum.[23]

The complete syndrome established by Lindau also includes cystic changes in the pancreas and kidney, tumors of the epididymis and ovary, angiomatosis of the liver and hypernephromas. These abdominal lesions rarely cause symptoms, and diagnosis of the complete syndrome must await post-mortem examination. However, the clinical diagnosis of Lindau's disease or von Hippel–Lindau disease seems justified when a definite hemangioblastoma of the retina is associated with a surgically verified hemangioblastoma of the central nervous system.[22, 32]

This discussion has reviewed the salient histologic features of angiomatosis retinae and stressed the relation between hemangioblastomas of the retina and co-ordinated neoplastic changes in the central nervous system and somatic organs. The close clinical and histologic alliance of von Hippel's angiomatosis retinae with the systemic changes described by Lindau necessitate extensive follow-up examination of patients presenting any portion of the syndrome known as von Hippel–Lindau disease.

Summary

Angiomatosis retinae is defined as a comparatively rare disease characterized by one or more hemangioblastomas of the retina.

The incidence of the disease is reviewed, and the clinical evolution of the process summarized.

Treatment is outlined with attention to radiation therapy and destruction of the tumor with electrosurgery.

A case of angiomatosis retinae in a twenty-nine-year-old man is reported. The process was confined to the left eye, which disclosed a globular, red-pink tumor mass served by an immensely dilated retinal artery and vein. This tumor was treated with diathermy, and the lesion became white though the size of the mass was not changed and the vessels remained somewhat enlarged.

The pathology of hemangioblastomas of the retina is described, and the relation between these tumors and comparable neoplastic changes in the central nervous system is stressed.

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ACUTE LUMBAR EPIDURAL ABSCESS

Report of a Case

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THE diagnosis of an acute abscess of the spinal epidural space is rarely made before onset of neurologic signs, in spite of the fact that the severe back pain generally causes the patient to consult a physician before irreversible neurologic disabilities develop. A case is reported below to re-emphasize the importance of the syndrome of severe back pain, with local spinous tenderness, fever and leukocytosis. Early surgical intervention, combined with antibiotics, makes the prognosis of this disease less serious.

CASE REPORT

A 26-year-old sergeant entered the United States Army Hospital, Camp Gordon, Georgia, on September 24, 1952, because of chills, fever and severe pain in the lower back. He had been in excellent health until 3 days before admission, when he first noticed a mild pain in the lower back that did not prevent sleep. On the following day the pain became more severe and was exaggerated by walking, sitting, coughing or any movement of the back. That night the patient slept little, finding no comfortable position to alleviate the back pain. In the evening before admission he was examined in the emergency clinic, where novocain was injected into the back and codeine given for the pain. These measures gave no relief, and during the night he had a shaking chill with fever. Early the next morning he was hospitalized. At no time was there radiation of the pain, which was localized over the right sacroiliac joint. He had no urinary symptoms.

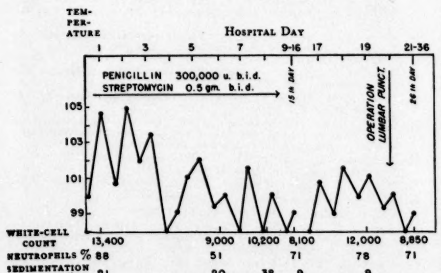

FIGURE 1. *Course in the Hospital.*

Eighteen days before admission he had had several "boils" on the neck. He had had malaria during World War II with no recurrence.

Physical examination revealed a tall, slender, muscular, acutely ill man who was restless and complained continuously of severe back pain; he repeatedly asked for something to relieve the pain. There was exquisite point tenderness in the region of the right sacroiliac joint, tenderness over the 4th lumbar vertebra and pain bilaterally on vigorous straight-leg raising. Otherwise, the examination was negative.

The temperature was 102°F.

Laboratory study disclosed a white-cell count of 13,400, with 88 per cent neutrophils and 12 per cent lymphocytes. The erythrocyte sedimentation rate (Wintrobe method) was 21 mm. per hour; other blood studies, including smears for malaria, were negative. Several blood cultures were sterile. Urinalysis showed a specific gravity of 1.026, a ++ test for albumin, no sugar or bile and only an occasional white blood cell per high-power field in the sediment. Radiologic examinations of the chest, abdomen and sacroiliac region were negative.

After several blood cultures had been obtained administration of aqueous procaine penicillin, 300,000 units, and streptomycin, 0.5 gm. twice daily, was immediately begun. The temperature continued to spike, and a shaking chill occurred on one occasion during the 1st 3 hospital days. Then the fever gradually subsided, until the patient was afebrile on the 8th day (Fig. 1). During the first 4 hospital days codeine sulfate, 0.064 gm. every 4 hours, and at times meperidine hydrochloride, 0.075 gm., were used to control pain. However, by the 8th hospital day, no medication for pain was necessary.

On the 7th hospital day the diagnosis of epidural abscess with or without perinephric abscess was made on clinical grounds. Consequently, antibiotics were stopped, and a urologic consultation obtained. Intravenous and retrograde pyelograms revealed slight widening and flattening of the kidney calyxes, suggesting mild congenital polycystic disease of the kidneys; this was thought to be the explanation of the albuminuria.

Between the 8th and 16th hospital days, the patient was asymptomatic and afebrile, required no medication and was taking physiotherapy. On the 17th hospital day fever and back pain again developed. Three days later, because of local tenderness over the 3d and 4th lumbar vertebras, a lumbar puncture was done with extreme caution. As the needle was slowly advanced between the 3d and 4th lumbar vertebras constant suction with a 5-cc. syringe was maintained. When the epidural space was entered, 1 cc. of thick, yellow pus was aspirated, and the needle immediately removed. The diagnosis of acute lumbar epidural abscess was confirmed. An emergency laminectomy of the 3d and 4th lumbar vertebras was performed on the 20th hospital day, with complete removal of a partially localized abscess. A minute opening was accidentally made into the dura, and this was sealed with Gelfoam soaked in aqueous penicillin, 1000 units per cubic centimeter. Also, a partially localized abscess of the right paraspinal muscles was found and excised as completely as possible. The wound was left open and packed loosely with sterile gauze. The incision granulated from the bottom and was subsequently closed secondarily. There was never any evidence of meningitis or any neurologic complication. The organism found at operation as well as on epidural puncture was hemolytic *Staphylococcus aureus*. Microscopical studies of the excised laminae showed the bone to be normal, and bacteriologic culture demonstrated no growth.

DISCUSSION

Cases of spinal epidural abscess have been repeatedly reported since 1820[1] under various names such as perimeningitis spinalis, peripachymeningitis, epimeningitis spinalis, pachymeningitis spinalis, meningitis spinalis externa and purulent perimeningitis.[2] Finally, Dandy's[3] paper in 1926 clarified the anatomy of the epidural space, as well as the symptomatology, diagnosis and treatment of future cases; at that time the mortality was 100 per cent. Slaughter, Fremont-Smith and Munro,[4] in 1934, were the

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first to report a case diagnosed before onset of neurologic symptoms. Subsequently, Cohen,[5] Stanley,[6] Van Den Berg,[7] and Kaplan and Lautkin[8] reported cases diagnosed before neurologic signs appeared. However, in each of these cases, except for that of Slaughter and his associates,[4] the patient had clinical evidence of meningitis, with a stiff neck and a positive Kernig sign, and Cohen's[5] patient had hyperesthesia over the eleventh and twelfth thoracic segments. The only neurologic sign in the case reported above was exacerbation of the back pain on vigorous straight-leg raising.

The epidural space is the area between the bony wall of the vertebral canal and the dura covering the spinal cord. It extends from the foramen magnum to the sacrum and contains only fat, loose areolar tissue and numerous veins. The ventral aspect of the dura of the spinal cord is attached to the bone and the ligaments of the vertebras from the foramen magnum to the second sacral vertebra. Consequently, the epidural space exists only dorsal and lateral to the spinal cord until the level of the second sacral vertebra where it completely surrounds the dura of the spinal canal. Dandy[9] found that the space was only a potential space until about the seventh cervical vertebra, where it gradually enlarged until a depth of 0.5 to 0.75 cm. was reached between the fourth and eighth dorsal vertebras. The space again gradually becomes smaller, especially over the eleventh thoracic and second lumbar vertebras, only to enlarge again over the remaining vertebras and reach its greatest size at the level of the second sacral vertebra, where it completely surrounds the dura. The space might be said to vary inversely with the size of the spinal cord and its large mass of nerve roots given off in the cervical and lumbar regions.

Infection enters the epidural space either by direct extension from adjacent tissues, such as decubitus ulcers, wounds of the back, perinephric or psoas-muscle abscesses and osteomyelitis of the spine, or by metastasis from any infection such as furuncles of various parts of the body,[9] mastoiditis, peridontal abscesses, cystitis, acute upper respiratory infection and cellulitis. Case reports indicate that metastatic infection by way of the blood stream occurs most commonly, and that furuncles and carbuncles of the skin are the most frequent precursors. Hemolytic *Staph. aureus*[2] is the usual organism found, but pneumococci, streptococci, *Salmonella typhosa*, brucella,[10] *Pseudomonas aeruginosa* and actinomyces have been isolated at various times. Some writers[11, 12] believe that osteomyelitis of the vertebras precedes the epidural abscess in almost all cases of metastatic infection. This makes it difficult to explain the rarity of anterior abscesses, or just why the metastatic infection affects the dorsal segments so much more frequently than the anterior. It is suggested, however, that repeated mild trauma to the dorsal segments produces some local vascular changes that give these segments a predilection for being the site of a metastatic infection.[11] In the case reported above, no osteomyelitis was found.

The diagnosis of acute spinal epidural abscess is not difficult. Like those of an abscess elsewhere in the body, the cardinal signs are pain, fever and localized tenderness. The pain is sudden in onset, severe, almost unbearable, accentuated by any motion of the spine and frequently not relieved by repeated doses of a narcotic. The temperature is usually 100 to 104°F., with a white-cell count of 12,000 to 25,000.[13] Severe local spinous tenderness designates the level of the epidural abscess and makes myelograms unnecessary. If no diagnosis is established with these cardinal signs neurologic changes such as paresthesia or dysesthesia, paresis, paralysis and incontinence develop. Boharas and Koskoff[13] reported that the interval between onset of pain and development of neurologic signs varies from two to forty days, with an average of six and a half days. In addition to these diagnostic signs, there is usually a history of local infection such as a furuncle preceding the onset of pain. Boharas and Koskoff, again, found the interval between the history of an infection and the onset of back pain to be a few days, weeks or years, with an average of four and two-tenths weeks.

Study of the spinal fluid[2] is not always advisable or helpful. The fluid may be entirely normal or (as in most cases) may show a moderate elevation of protein and cellular content. Manometric studies usually demonstrate a partial or complete block but may be entirely normal. It is highly debatable whether the patient should be subjected to a lumbar puncture, especially if there is no meningitis. In experienced hands and with constant aspiration on the spinal needle, it is possible to obtain pus from the epidural space without causing a purulent meningitis.

It seems much more advisable to operate without risking a purulent meningitis, because no other disease produces such severe back pain with local spinous tenderness, fever and leukocytosis. The condition is just as much a surgical emergency as appendicitis, and treatment should be just as ardently pursued.

The prognosis at present depends on early diagnosis and immediate laminectomy of all vertebras overlying the abscess to institute adequate drainage. Without operation the mortality has been 100 per cent.[3] Abrahamson[14] presented 60 collected cases in 30 of which operation was performed, with survival of 20 patients. In the 30 cases in which no operation was performed there were no survivals. Bunch and Madden[15] report an operative mortality of 25 per cent, whereas Gasul and Jaffé[16] found a mortality of 51.3 per cent in 35 cases. Boger,[2] in reviewing the literature, described 84 cases in which

operation was performed, with a mortality of 33 per cent. Complete recovery depends on immediate treatment because the return of function after onset of paralysis and incontinence is negligible, especially if they have been present for any duration of time. Echols[12] states, "If the diagnosis is delayed until paralysis has been complete for a number of days, operation is usually contraindicated."

It is interesting that the patient described above had become afebrile and almost completely asymptomatic after one week of penicillin. No doubt the location of the abscess was a significant factor in preventing the development of neurologic signs. It is also believed that the penicillin was beneficial, but it would probably not have replaced the old axiom that the only cure for an abscess is adequate drainage.

To facilitate differential diagnosis acute spinal epidural abscesses might be considered to present two stages. The first is that of extremely severe back pain, fever, leukocytosis and localized spinous tenderness. The second stage is the development of neurologic findings such as sensory changes, motor paralysis and incontinence.

Acute suppurative meningitis, perinephric abscess, acute back strains and rheumatoid spondylitis are probably the most frequent diagnostic problems that simulate the first stage of an epidural abscess.

Acute suppurative meningitis is not usually associated with such severe back pain and local spinous tenderness. Mental confusion and nuchal rigidity are prominent features of purulent meningitis but not of epidural abscess. Furthermore, examination and comparison of the cisternal and the lumbar spinal fluids are found identical and abnormal in suppurative meningitis; in epidural abscesses the cisternal fluid is normal, whereas the lumbar fluid may or may not be abnormal. Here, again, if epidural abscess is considered possible, a lumbar puncture is probably inadvisable. Purulent meningitis may be a complication of epidural abscess especially when produced by passage of a spinal needle through an infected epidural space into the spinal canal. However, the correct diagnosis is still apparent when one considers the triad of excruciating back pain preceded by a history of some type of local infection, exquisite local spinous tenderness and evidence of an infection — that is, fever and leukocytosis.

Perinephric abscess and rheumatoid spondylitis can usually be differentiated by the history and physical findings. If not, radiologic studies of the kidneys and sacroiliac joints will distinguish an epidural abscess. Acute back strain usually improves with bed rest, heat and salicylates and does not cause fever and chills.

The second stage, during which neurologic signs develop, may be confused with such diseases as acute poliomyelitis, acute transverse myelitis, tumors of the spinal cord and an embolus or thrombus of the spinal vessels. Poliomyelitis does not produce sensory changes, and lumbar puncture does not reveal pus or a subarachnoid block. In acute transverse myelitis a systemic disease is usually present such as one of the exanthems, syphilis, tuberculosis or a postvaccinial reaction, and the neurologic signs tend to be disseminated. The cardinal signs of the epidural abscess, the preceding suppurative lesion and the localized spinous tenderness are absent.

The acute onset of pain and the fever, with rapid progression of paralysis, should not cause confusion with the slow progression of a spinal-cord tumor, and even the rare hemorrhage into a spinal-cord glioma or an angioma is differentiated from epidural abscess by absence of high fever, chills, leukocytosis and localized spinous tenderness. Thrombosis of the spinal vessels is usually characterized by sudden onset of paralysis, with no latent period like that in epidural abscess. Furthermore, no spinal block or pus is found on lumbar puncture.

Summary

A case of lumbar epidural abscess diagnosed before the development of any neurologic signs is presented. The syndrome of severe back pain, local spinous tenderness, fever, and leukocytosis is reiterated to facilitate early diagnosis, treatment and cure of an otherwise fatal disease.

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SPECIAL ARTICLE

MEDICAL PRACTICE IN THE COLONY AND PROTECTORATE OF KENYA

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NAIROBI, KENYA

KENYA is a young and developing country. The progress made during the last eight years has been phenomenal, and medical services have shared in it. From the Capital to the most distant rural African areas the program of medical development has been going on at great speed. It has, in fact, outstripped the economic, educational and social development of the African, thus leading to heavy population pressure.

In rural areas, under the auspices of the local African councils, dispensaries and maternity services have been expanding to accommodate the increasing demand due to the increasing consciousness of the indigenous population of the benefits of Western medicine. The average African has become doctor-minded and has great respect for the "medicine man." If he can afford it, he is willing to seek the best medical attention. This point will have to be taken into consideration when future planning of specialist services for the African is envisaged. The African of today is willing to pay for good services rendered.

Besides the African, there is an immigrant population of about 150,000 composed of Arabs, Asians and Europeans. The last have been mainly instrumental in giving the impetus to the rapid and spectacular growth of the country in the last half century.

The recent Mau Mau disturbances have caused the country to be much upset and perturbed; for sixteen months or more there has been such retardation of progress. The prospect of a better future, however, is still there.

KENYA COLONY AND PROTECTORATE

The British Colony of Kenya, situated in Eastern Equatorial Africa, is bounded on the north by Abyssinia and the Sudan, on the west by Uganda and the great Lake Victoria (the third largest in the world), on the south by Tanganyika Territory and on the east by the Indian Ocean and a part of Italian Somaliland. The total area is 224,960 square miles, of which the water area is 5230 square miles. The territory was formerly known as British East Africa Protectorate. In July, 1920, the Protectorate, except for the coastal strip under the dominion of the Sultan of Zanzibar, was raised to the status of a Crown Colony under the title of Kenya Colony. Its capital is Nairobi, and Mombasa is its main port.

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Nairobi, the largest center of population, is 5495 feet above sea level. It has a population of 134,465 people, composed of 10,830 Europeans, 43,635 Asians and 80,000 Africans.

Mombasa is the second largest center in Kenya and serves as the main port for Uganda and part of the Belgian Congo as well. Its population of 101,907 consists of 2027 Europeans, 26,306 Asians, 13,485 Arabs and about 60,000 Africans.

The total population of all the races of Kenya is about 5,373,078 which includes 29,660 Europeans, 101,012 Asians, 24,174 Arabs and 5,218,232 Africans.

Climate

The colony is divided into two zones by climate: the Lowland, which covers the area below 4500 feet, and the Highland, which includes the area above 4500 feet reaching to and above the snow line on Mount Kenya (17,000 feet).

The Lowland zone comprises the hot, humid coastal belt on the east, the huge desert-like Northern frontier province and the area around the great lake that lies 3500 feet above sea level on the west. The Highland area, of some 16,700 square miles, has a cool, bracing and healthy climate.

The hottest months are January, February and March, and the coldest July, August and September. The rainy months are March, April, May and part of June, November and December. The average annual rainfall is 35.53 inches.

MEDICAL SERVICE AND PRACTICE

The medical history of the country may be divided into three phases. The first, or pioneering, phase was the curative side of medicine that originally held the field, to care for the Government officials and the military who were opening up the country, as well as their subordinate Asian and African employees. Some medical missionaries came as part of their societies' evangelical programs, and some hardy private practitioners, both European and Asian, joined the early settlers.

The second phase saw the introduction of the preventive as well as the curative side of medicine and the erection of a few hospitals. Settlers were coming in and immigrants came from India, and with them came more and more physicians. It could be called the era of the Jack-of-all-trades, in which every doctor had at times to be prepared to deal with all branches of medicine. It was during this phase that the laboratory services were developed,

and toward its end radiology was introduced. Today, medical practice is in the early stages of the third phase when specialized services are finding a call for their employment and the hospitals and ancillary services are being developed on the most modern lines.

Government Medical Service

The history of the health services in the East African Protectorate during its early years is chiefly that of the health and care of the European officials, who during the process of opening the country had to be protected against the dangers to health in an entirely uncivilized tropical country.

The main spearhead of civilization was the Uganda Railway, which stretched over 500 miles from the coast to the great lake, and the staff of the Medical Department was distributed entirely along the line of the railway. Since the primary function of the Department was the care of the Government servants, in 1913, 16 out of the 22 members of the staff were distributed along the Uganda Railway, 3 were on the Northern Frontier for military duty, 2 were at the coastal towns of Lamu and Kismayu, and 1 was in the African Reserve.

Professor W. J. Simpson visited the East Africa Protectorate in 1913, to examine the sanitary conditions of the country and to suggest the policy that the Government should adopt. He advised on the public-health ordinance and recommended additional personnel to care for the health of the African population. Because of World War I it was only in 1920 that sufficient personnel were available for the African rural areas. The system adopted was to establish a central hospital with small dispensaries in the neighboring districts in charge of trained African dressers. Up to 1925 the onus of maintaining the health and welfare of the general population of all races and the improvement of the conditions under which they lived fell on the Medical Department. In 1929 the local native councils were created. They became responsible for additional aid in the form of medical facilities for their people.

Kenya being a young country, the demand for medical services has been growing each year. The Medical Department was still undertaking the bulk of the needs of the three sections of population up to the outbreak of World War II. It operated most of the hospitals, the laboratory services, child welfare services, maternity clinics, dispensaries and a medical training school for African hospital assistants. Since that time the great increase in private medical services has adjusted the balance.

The European section of the population has gradually taken over all the hospital facilities in the Highland areas and is sharing some of the responsibility of that function with the Government in the Lowland areas. The Asian population, as far as the main centers are concerned, is adopting the same responsibilities; consequently, there are well matured plans for the erection of first-class hospitals. A similar development has occurred in the larger local governmental bodies such as the Nairobi City Council, which is negotiating with the central Government with a view to taking over all the dispensaries and welfare services within its boundaries.

Laboratory Services

The Medical Research Laboratory is situated in the Capital; it has extensions in all major areas of the country in the form of small laboratories under Africans trained at the center. These subsidiary services provide for a limited amount of routine work, but it is in the central laboratory that the high standard of research is maintained, with much benefit to the adjoining territories.

Specialist services. With the growth of the country the demand for a higher standard resulted in the development of the Government specialists. These are specialists in surgery, ophthalmology, medicine, psychiatry, anesthesia and so forth. Among their duties is the training of the rising generation of Africans who are adopting medicine and its ancillary services as a career. Although these specialists are to a great extent centered in the Capital, they are available to the country districts; at the same time younger men with special qualifications are being appointed to the other towns.

Medical training center. With the expansion of medical services to meet the needs of the rural population, it was found necessary to increase the training of the African personnel. This was possible only through the increased number of educated Africans that became available with the advance of education among them. Africans are being trained in Kenya as hospital assistants, nurses, health inspectors, laboratory assistants, orthopedic assistants and assistants to radiologists. The more highly educated Africans of university standard are being sent to Makerere College in Uganda for training that is within measurable distance of a full medical course comparable with those in the world universities.

Local Government Health Services

In the larger towns the African maternity hospitals, European and Asian child welfare, Asian maternity and venereal-disease clinics for Africans and other services are undertaken by the local authority, among whose councilors all three races are represented.

In the rural areas the local African councils are beginning to accept more and more responsibility for the cost of extra medical services.

Mission Medical Services

The Christian missionary societies were among the pioneers of medical services to the African.

They offered medical and hospital services at their stations to the local inhabitants. The Government recognized their contribution by grants-in-aid. Many of the hospitals are well equipped and well staffed.

Private Practice

By the end of 1951, 776 persons were registered as medical practitioners in the Colony. Two thirds of these are in private practice, and half are Asian doctors qualified in India. With the growth of private practice, medicine is gradually assuming the character that it has in older countries, where the bulk of the curative side is undertaken by the private practitioner and most of the preventive aspect is undertaken by the local or central government as far as the immigrant population is concerned. Among the Africans there is also a growing appreciation of what the private practitioner has to offer. Private practice is approaching still further the character assumed elsewhere by the development of its two aspects — the general practitioner and the consultant or specialist. The two sides are more fully developed among the European section but are beginning to appear among the Asians as well. As a consequence of these developments medical practice in Nairobi is attracting men from areas well outside the East African territories. The standard of qualification is rising, and with it the standards of the hospitals and nursing homes among the two major immigrant populations.

The result is a heavy cost of medical care for the average person. To meet this the European community has established a hospital service scheme, administered by the central government and contributed to by the whole European community on a compulsory basis. The contribution is collected with the income-tax assessment and is graded according to the tax. The success of the scheme has led to an inquiry into the possibility of a similar scheme for the Asian community. The fund so accumulated pays 25 shillings a day toward the contributors' hospital fees, 20 shillings a day toward nursing fees and 200 shillings for maternity benefit (the contribution provides about three fourths of the cost of those services).

The tendency is for physicians to work together in the form of a group practice, generally termed "firms." This is more pronounced among Europeans. The Asian doctors are still much more individual workers, although a similar tendency is beginning among them.

Some of these firms include one or more who have specialist qualifications. Others are either groups of general practitioners or specialists who work together for convenience and companionship.

In practice there is a great deal of interdependence among the Government medical service, the Asian private practitioners and the European practitioners. There is a free choice of doctors for all the races and there is little or no racial discrimination; yet each racial group goes to the hospital designated for its members.

Problems of Practice

The service of medicine in the Colony follows the racial divisions of the population. It is an arrangement based on the present state of social and racial development in the Colony, but it creates a complicated machinery and is economically unsound. Undoubtedly, a strain is imposed on the financial resources of the country, both public and private. Medical practice follows the pattern of contemporary society, and there is no evident alternative, but change is in the air.

The European population can be divided into officials and civilians. The latter to a great extent intend to make the country their homes, whereas the majority of the former are transients, owing allegiance to the Colonial Service throughout the world. The civilians or settlers, make up the greater proportion of the white population. They find that the cost of modern medicine lies heavily upon them although the Hospital Fund helps to some extent. Very few Europeans represent the industrial or artisan classes of older countries, so that whereas there are a number of poor and indigent, the average European has a higher standard of living than in Europe and consequently finds his income chasing his expenditure in an increasing spiral.

Among the Asian community the contrasts are far greater. Some of them include the wealthiest people in the country, but the great majority are among the poorest — poorer in one sense than many Africans. The cost of medicine is high in relation to income, and the cost of hospitalization beyond the average Asian's means.

For the Africans there are no private hospitals. The entire African population must depend on Government hospitals, except for the mission hospitals. The wealthier African has no alternative accommodation. Of course once he is admitted to a Government hospital his private practitioner ceases to be able to attend to him; in the hospital he has no choice of doctor.

So far private practice has been the prerogative of the European and Asian doctor. The time is rapidly approaching when the first African physicians will be setting up practice. There is no doubt that a great proportion of the population find racial barriers irksome and frustrating, and the time is approaching when the old, rigid racial pattern will have to be replaced by a new one, and medicine may well lead the way.

With the increase in educational facilities and the increasing number of Africans who can avail themselves of it, the standard of living of the African is rising. He expects a correspondingly higher standard of medical treatment. There is a new grading

of the African society, away from the old tribal sanctions: a society based on culture, capacity and income. Those who belong to the new upper classes are in the awkward position of having only the Government hospitals to go to when they are sick, and with a few exceptions they are classed with the ignorant and the more primitive of their fellows. The time has come when this difficulty has to be understood and be met, for Africa is rapidly emerging from its past.

The problem is one that intimately affects medical practice. The social structure of the population is thus made of three "classes" that are at the same time racial groups: the European, who has brought into a primitive country a high standard of living and whose average income is high; the Asian, who varies from the very rich to the very poor and whose whole orientation is eastern and his demands on life small, though he has a great capacity for industry and so is able to compete easily with both the European and the African in the same fields (today the younger generation, educated in the western ways, is rapidly raising the Asian standard of living); and the African, whose culture was that of a primitive people until the impact of Western civilization at the beginning of this century roused the native from his past. During the last twenty years his whole outlook has changed rapidly. Both the African and the Asian are trying to raise their standards socially and economically, and naturally they expect the same treatment as their European counterpart. The position is an invidious one. It is taxing the best brains of all races and the goodwill of those in authority as well as those who aspire to share it with them. The problem is a moral and spiritual one — of the emotions, of tradition and of culture. With the vast social, economic and intellectual changes that have taken place, a common objective needs to be developed — to use a modern term, an ideologic counterpart is needed to which all men of goodwill could subscribe.

The medical aspect is but a cross section of the world struggle of the times, and many physicians in Kenya are seeing their profession as a means of demonstrating the basis on which a multiracial society can successfully live together.

MEDICAL PROGRESS

A DECADE OF PROGRESS IN THE Rh BLOOD-GROUP SYSTEM (Concluded)*

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Significance of f

At present it is difficult to assess the practical importance of the antigen, but of its academic importance there can be no doubt. Perhaps the practical status of the new antigen and its corresponding antibody can best be appreciated by the realization that many examples of currently used anti-c and anti-e typing serums probably also contain anti-f, which heretofore had been undetected. The ease with which the anti-f can be isolated from these serums, together with the fact that its existence has escaped notice for several years, constitutes a strong argument in favor of the supposition that its recent discovery will have little or no effect on the interpretation of cell-typing results at the clinical level. At present it seems that f by itself is a poor antigen. Persons of genotype CDe/cDE, if suitably stimulated, would be expected to produce "pure" anti-f. During the past decade many thousand susceptible recipients must have received transfusions of f-positive blood, but only within recent months has the first example of "pure" anti-f been found. In contrast to this, our evidence indicates that a synergistic effect exists between the antigens c and f and the antigens e and f when persons lacking c or e are exposed to the dual stimulus. In other words, a CDe/CDe person immunized with blood containing both c and f antigens will respond to f as readily as to c, but a person of Type CDe/cDE (that is, one incapable of making anti-c), when exposed to blood containing both antigens, will respond to the f antigen only very rarely. This situation has a precedent in the Rh system in the shape of the pattern of response obtained by stimulation of susceptible persons with the C antigen. Anti-C in the "pure" state is rarely made in these circumstances,[22] but exposure of a susceptible person to the combined antigens C and D frequently results in the production of anti-C together with anti-D.

Anti-f may be used to assist in the solution of a difficult problem frequently encountered when Rh genotyping tests are performed. A cell may be found

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that gives positive reactions with all five anti-Rh typing serums. Such a cell is usually classified as CDe/cDE because of the high frequency of this genotype (approximately 12 per cent) as compared with the low frequency of the alternative genotypes of cells giving the same reactions. On testing with anti-f these cells may be placed in one or the other of two categories, depending on whether they do or do not possess the f antigen. Table 6 lists the genotypes of cells (assumed to be CDe/cDE) in relation to their reaction with anti-f and shows that each of the two categories, produced by testing of such cells with anti-f, contains three members. In the f-negative category the commonest member is CDe/cDE, and in the f-positive category the commonest member is CDE/cde. These genotypes should therefore be the "first guess" when one is carrying out studies on isolated bloods.

TABLE 6. *Separation of Blood Containing the Rh Antigens C, D, E, c and e into Two Categories, Depending on Its Reaction with anti-f.*

BLOOD POSITIVE WITH ANTI-F	BLOOD NEGATIVE WITH ANTI-F
CDE/cde*	CDe/cDE*
CDE/cDe	CDe/cdE
CdE/cDe	cDE/Cde

*Most common genotype in each category.

It was pointed out above that the linked-gene hypothesis predicts the existence of chromosomes such as CDef in which the disturbance of the ce-gene combination is not accompanied by absence of the f antigen. If such chromosomes exist they may give rise to certain inaccuracies in Rh typing. As an example of the sort of error likely to be introduced, the phenotype of a hypothetical blood of genotype CDef/CDeF as determined by the usual five anti-serums will depend on whether or not the anti-c serum used for the test contains anti-f. If the anti-c serum used is "pure" the phenotype will be a true one, but if the anti-c contains anti-f the presence of the f antigen in the cells will give rise to a false-positive result with this serum and the blood will be wrongly regarded as possessing the c antigen. On this basis the blood will be misclassified as belonging to genotype CDe/cde. It is possible to calculate the frequency with which bloods will be misclassified in this manner for various assumed frequencies of the chromosome CDef. It is also possible, by examination of the existing data on Rh chromosome frequencies and by the assumption that the anti-c serum used in these studies contained anti-f, to show that the frequency of the chromosome CDef (or the "misclassified" chromosome) approximates 0. Deductions of this type, made from previously published data, tend to favor the position-effect theory since the postulation of a fourth pair of allelic genes makes it necessary to assign a finite value to the frequency of "misclassified" chromosomes.

The usefulness of anti-f serum in the fields of anthropology and medicolegal practice has not yet been explored. This serum enables one to identify two new types of Rh chromosome, the f-negative varieties of cde and of cDe, but the low frequency of these chromosomes and the generally close association between the gene combination ce and the f antigen will probably limit the value of anti-f in studies involving Caucasian-type bloods. It would be of great interest, however, to investigate the association between the antigen f and the chromosomes cde and cDe in non-Caucasian populations.

The medicolegal application of anti-f would consist in identifying the f-negative varieties of the chromosomes cde and cDe. A blood specimen of type CDe/cde (or CDe/cDe) that was f-negative could easily be differentiated from the more usual f-positive CDe/cde. In this way blood belonging to this common Rh type could be more exactly defined. These remarks also apply to blood typing carried out in cases of disputed paternity. Although it is unlikely that a paternity has ever been unjustly excluded because of the presence of anti-f in some Rh typing serums, it is possible that anti-f serum could be used in future to obtain just exclusion in certain cases.

There can be no doubt that the original definition of the f antigen was greatly facilitated by the use of Fisher's linked-gene theory. In the same way the development of the position-effect theory was dependent upon Fisher's concepts, for without linked genes, it is obviously impossible for a position-effect to exist. It would be rash indeed to assume that knowledge of the Rh system will not continue to grow in magnitude and complexity, but future developments will be more readily understood if they are viewed in the light of the linked-gene theory.

RH ANTIBODIES IN TRANSFUSION

The rise of knowledge of the Rh antigens has been dependent on study of the antibodies found in the serum of persons who have received blood transfusions or injections of blood and of antibodies found in the serum of women who have delivered an erythroblastotic fetus. At present it is not possible to prevent the isoimmunization against Rh that occurs in some pregnancies,* but, with very few exceptions, it is possible to avoid isoimmunization by transfusion. Some indication has earlier been given that the D antigen is by far the most important of the five readily recognized Rh antigens. The importance of D can be illustrated by an experiment carried out in this laboratory some years ago.

Twenty-two Rh-negative (cde/cde) volunteers were given repeated intravenous injections of Rh-positive (D-positive) whole blood, ranging in amount

*However, the risk of immunization to Rh is significantly diminished when there is an incompatibility of major (ABO) groups between mother and father.

from 500 cc. to as little as 0.1 cc.; the average interval between injections was three weeks. Within nine months 18 of the 22 volunteers had developed an anti-D antibody, the average period required for the development of immunity being five months. The 4 persons who did not develop anti-D were followed for eighteen months, during which they continued to receive injections, but even so no antibodies were found in their serums. It thus appears that approximately 20 per cent of healthy persons are resistant to an immunization procedure that readily succeeds in producing immunity in 80 per cent of a susceptible group. Unfortunately, there is no way of knowing in advance who will be susceptible and who will be resistant. Therefore an invariable rule must be made that D-negative persons must never receive D-positive blood by transfusion. It may perhaps seem unnecessary to reiterate this point, which has appeared many times in the literature of blood transfusion. Yet this department sees, each year, several cases of erythroblastosis among the first-born infants of Rh-negative women. These women have had the misfortune to be immunized against D by comparatively recent transfusions of Rh-positive blood.

Regarding the Rh antigens other than D the situation is less serious. Attempts to immunize volunteers against the antigens C, E, c, e and d showed that repeated injection of blood containing these antigens into susceptible persons only rarely produced an antibody response. Table 7 shows the Rh genotypes of the volunteers, the antigens with which they were injected and the numbers responding.

It will be seen that d was found to be the poorest antigen and c the best. These findings are borne out in clinical practice, in which anti-c is found to constitute about 1 per cent of all anti-Rh antibodies and anti-d is for practical purposes unknown. It is interesting that the cDE/cDE person who produced anti-e in this experiment was followed for over five years before the antibody was finally detected in his serum.

"Pure" anti-C is only rarely produced by D-positive persons. Two examples have been found by this laboratory, and Scorah and Aspinwall[22] have described others. Recently, we detected the exceedingly rare combination of anti-C plus anti-e in the serum of a woman of Type cDE/cDE who had received only 500 cc. of blood six months previously.

The presence of anti-c in the serum of a patient, although uncommon, is liable to lead to difficulties unless its nature is understood. It is not unknown for such patients to have received a transfusion of Rh-negative blood with disastrous consequences. On another occasion a baby with erythroblastosis caused by anti-c was given an exchange transfusion of Rh-negative blood, with the result that much more bilirubinemia and kernicterus developed. These dangers may be avoided by the realization that anti-c is only formed in persons who are homozygous at the C locus — that is, those who have 2 doses of the C antigen themselves lack the c antigen. The commonest genotype fulfilling this criterion is CDe/CDe, and it follows that this must also be the genotype of a donor who is to give blood successfully to a person who has formed anti-c.

The same general principles apply to the other, less frequent anti-Rh antibodies, anti-E and anti-e,

TABLE 7. *Results of an Attempt to Produce Various anti-Rh Antibodies in a Group of 75 Volunteers by Intravenous Injection of Suitable Red Cells.*

Antibody Sought	Antigens in Recipient	Antigens in Donor	No. of Volunteers Injected	No. of Volunteers Responding	Period Followed	Average Interval before Response
					mo.	mo.
Anti-C	cDE	C	14	0	13	—
Anti-D	cde	D	22	18	18	5
Anti-E	CDe	E	18	0	17	—
anti-c	cDe	c	9	2	10	10
anti-d	CDE	d	11	0	18	—
anti-e	cDE	e	1	1	84	72

but it may be stressed that the average blood bank will only rarely encounter these antibodies. A much more likely source of difficulty will be the anti-Kell antibody, first described by Coombs et al,[23] which is second to anti-D in frequency of occurrence.

Fortunately, it is not necessary exactly to identify an antibody in the serum of a patient before transfusion can be given (although it is often helpful to do so). Provided a crossmatch technic that is sufficiently delicate to assure complete compatibility is used, a transfusion may proceed regardless of the specificity of the recipient's antibody. There is only one crossmatch technic on which reliance can be placed, and this is the indirect antiglobulin (Coombs test) method, which is dealt with below.

Advances in Laboratory Methods

Until 1944 it was only possible to detect anti-Rh antibodies that agglutinated saline suspensions of red cells. At that time cases were known in which transfusion reactions had occurred without any detectable antibody in the patient's serum. Also, erythroblastotic babies were born to women whose serum appeared to contain no anti-Rh antibodies. These negative findings were obtained by the technic of incubating patient's serum with a saline sus-

pension of standard Rh-positive red cells, which was the only method in use at that time.

In 1944, however, Race[24] and Wiener[25] independently showed that the serum from such patients did in fact contain anti-Rh antibody but in a form that attached itself to Rh-positive cells without agglutinating them. This antibody, known variously as "blocking," "incomplete" or "univalent" antibody, was shown by the demonstration that it could be made to occupy the Rh-antigen sites of Rh-positive cells in such a way as to render them incapable of being agglutinated by a known agglutinating anti-Rh serum. This was the principle of the "blocking test" used for the demonstration of incomplete antibodies until Diamond and Abelson[26] showed that a simple slide test using a heavy plasma suspension of Rh-positive cells was capable of demonstrating these antibodies with great reliability. This test led to the use of high-protein mediums such as 20 per cent serum albumin as enhancing or potentiating agents in the detection of incomplete antibodies by direct agglutination methods. Wiener[27] has employed the term "conglutination" to describe the effects of such substances (including normal human serum) in causing the agglutination of cells coated with incomplete antibody. We are unable to subscribe to the use of this term since it bears a prior and quite different definition in other fields of immunology. Substances other than serum proteins were tried as enhancing agents; examples of these are gum acacia, gelatin, dextran and PVP,[28,29] but none of them gained general acceptance as routine reagents.

The greatest advance of all in the field of antibody detection came with the development of the antiglobulin reaction by Coombs, Mourant and Race.[30] This reaction, customarily known as the "Coombs test," is a method for detecting the presence of human globulin on the surface of an erythrocyte. The principle on which it depends is that normal erythrocytes are not agglutinated by the addition of an anti-human globulin serum but cells that are coated with human antibody globulin are agglutinated by this serum. An essential proviso is that the reaction is performed in the absence of dissolved human protein, which, if present, would "divert" or "neutralize" the antihuman serum before it had an opportunity to react with human globulin fixed to the cell surface. The test involves at least three washings of the cells being tested and is thus somewhat tedious, but there can be no doubt that the great delicacy of the reaction makes any additional labor expended in its performance worth while. Recently, a simple centrifuge has been described[31] that permits up to 12 Coombs tests to be performed in about two minutes, and thus the time factor is no longer a valid argument against use of the test for routine antibody detection and crossmatching.

The next advance in the field of laboratory methods came with the development by Morton and Pickles[32] of the trypsin-modified cell technic. They showed that red cells after incubation with a suitable solution of trypsin became readily agglutinable by incomplete anti-Rh antibodies. The method is simple and reliable and is widely used as a screening test in laboratories that carry out a large number of antibody tests. It is not, however, to be recommended for the performance of isolated tests.

It is not possible to advocate wholeheartedly the use of any one of the available technics for antibody detection or crossmatching. Each method has its advantages and disadvantages. For instance, the slide test is rapid and simple but lacks the precision and delicacy of the antiglobulin reaction, which in its turn requires exact attention to technical detail. Ideally, a combination of methods should be used, one of which should be the antiglobulin test.

Prenatal Management of Erythroblastosis Fetalis

Advances in the prenatal management of erythroblastosis fetalis have been few in comparison with the improvements in the care of newborn infants. The most important feature of prenatal care at present is the detection of sensitization to Rh in Rh-negative women, and there has been improvement in this, with better methods for detection of sensitization, a great increase in the number of laboratories competent to perform the tests and a widespread acceptance among the medical profession of the necessity for such tests. It is now recognized that all Rh-negative women, including primigravidas,[33,34] should be tested during pregnancy for sensitization to the Rh factor. In routine cases, a test is advised at twenty-eight to thirty weeks, being repeated at thirty-five to thirty-seven weeks if the first is negative. If there is a history of previous blood transfusion, early or severe jaundice, neonatal anemia or stillbirth in a previous pregnancy, a test for antibodies should be done at the first prenatal visit. If sensitization is discovered it is frequently desirable to retest at intervals to ascertain if the titer is rising, and always desirable to do subgroup testing on the husband and his parents, and any living children, to determine if possible the "zygosity" of the husband.

There has been much improvement in the degree of understanding of the problem of erythroblastosis by the medical profession as well as the public, and therefore less hysteria. There has been some progress in the direction of understanding the basic physiologic pathology of erythroblastosis, but a great deal remains to be learned about the mechanisms of red-cell destruction and replacement, fetal hydrops and bilirubin metabolism. The hope for the future that erythroblastotic stillbirths can be prevented depends greatly on more accurate knowledge of the problems involved. To date, the

history of attempts to prevent stillbirth is a succession of failures — "competing" antigens, vitamin E and progesterone, vitamin C, Allergesil, methionine, Rh Hapten, stilbestrol and, most recently, ACTH and cortisone.

Early delivery of the baby in selected cases has been advocated for many years. Experience with this procedure in the years before 1949 was generally that total fetal salvage was less with early delivery and brain damage more frequent, the greatest hazard being the increased frequency of brain damage in premature infants. Since the demonstration that brain damage is preventable by proper postnatal care it is now possible to use early delivery to prevent a certain number of stillbirths. The greatest difficulty here is to know which babies would profit by early delivery and which would do perfectly well without it and be better off for the increased degree of maturity. Prematurity is still a considerable hazard, especially in babies with erythroblastosis, even though the brain damage can now be prevented.

A better understanding of the prognosis has been helpful in the prenatal management of erythroblastosis fetalis. Most important is the realization that in no case is the prognosis hopeless, even when there have been several stillbirths in succession and the husband is homozygous for the blood factor involved. It is well known that the prognosis is much better, but not necessarily good, when the maternal titer is low and much worse, though not necessarily poor, when the maternal titer is very high. There is a strong tendency for repetition of the severity of disease in subsequent babies, but there is also an unexplained tendency to great variation in either direction that makes accurate prognosis impossible in the majority of cases. Again, increased knowledge of the fundamental factors involved will improve the ability to prognosticate if not actually to influence the prognosis by specific action.

TABLE 8. *Results of Improved Therapy of Erythroblastosis Fetalis in a Maternity Hospital (Boston Lying-in Hospital).*

PERIOD OF STUDY	STILLBIRTHS	EXCHANGE TRANSFUSIONS OF LIVING INFANTS	MULTIPLE EXCHANGE TRANSFUSIONS OF LIVING INFANTS	USE OF FEMALE BLOOD DONORS	GESTATION OF LESS THAN 38 WK.	RECOVERIES WITHOUT SEQUELAE	CASES OF KERNICTERUS	CASES OF TYPICAL HYDROPS*	DEATHS FROM OTHER CAUSES*
				%	%				
1/1/45–10/31/46	10 (24%)	0	—	—	52	18 (58%)	8 (26%)	3 (10%)	2 (6%)
11/1/46–3/31/49	21 (33%)	30 (70%)	0	26	52	32 (76%)	6 (14%)	2 (5%)	2 (5%)
4/1/49–6/30/51	14 (30%)	21 (66%)	3 (9%)	94	28	26 (81%)	1 (3%)	4 (13%)	1 (3%)
7/1/51–6/30/53	13 (22%)	29 (64%)	5 (11%)	85	24	38 (84%)	0	4 (9%)	3 (7%)

*No kernicterus.

POSTNATAL MANAGEMENT OF ERYTHROBLASTOSIS FETALIS

In the past nine years there has been notable progress in the care and treatment of the newborn infant with erythroblastosis fetalis. The complete reconvery rate has improved from 58 per cent to over 84 per cent (Table 8), and, more important in some respects, the development of kernicterus was reduced from 26 per cent to 0 in this series of 170 cases.

Kernicterus, or damage to the nuclei of the brain had, in the past, resulted in such a large number of infants with mental retardation, nerve impairment and especially muscular inco-ordination that of the 10,000 cases of cerebral palsy estimated to occur in this country every year, about 1000 were probably due to this complication of hemolytic anemia of the newborn. The prevention of kernicterus, therefore, was a real achievement and depended basically on the fact demonstrated by Vaughan et al.[35] in 1949 that the damage to the brain does not occur until a day or more after the baby's birth. In 1950 it was shown that kernicterus is directly related to severity of jaundice,[36] and in 1952 it was demonstrated that high concentrations of bilirubin were the probable precipitating factor.[37]

Immediately after the birth of the infant with erythroblastosis fetalis the patients most severely affected may show profound anemia, marked splenomegaly and hepatomegaly, and generalized edema, particularly with marked ascites in the abdomen. The heart is usually dilated, its action rapid and feeble (which, together with the other signs, suggests rapidly increasing cardiac failure), and there may be petechiae and ecchymoses all over the body. This tendency to congestive heart failure in severe erythroblastosis at birth was first noted by Mollison and Cutbush[38] in 1949. The infants with typical hydrops fetalis have invariably died, but there is an important group, perhaps 10 per cent of all cases, in which there is evidence of congestive heart failure without true hydrops, and most of these patients can now be saved. The most successful method of treating or preventing further decompensation has been the reduction of blood volume during the course of exchange transfusion. This is done by removal of more blood from the baby's circulation via the umbilicus than the amount given during the course of the first part of the exchange transfusion. The deficit is dependent on the response of the venous blood pressure, which one measures directly

at frequent intervals by holding the plastic catheter, which has been inserted in the umbilical vein, in a vertical position above the abdomen. An attempt is made to lower the pressure to 60 mm. or less, while small amounts of donor's blood are being injected to improve the baby's anemia with blood containing a higher hematocrit than that which is removed. If the procedure is successful, even in seriously sick infants, the response is usually dramatic, improvement being observed during the course of the transfusion. Until about four years ago it was common practice to give more blood than was withdrawn, especially in very sick infants, and it is almost certain that some of the deaths in the early days of exchange transfusion resulted from increasing and untreated heart failure.

If the newborn infant with erythroblastosis fetalis does not have anemia or evidence of cardiac decompensation (and this is true of most of the liveborn infants) the most important consideration is the elimination of hyperbilirubinemia resulting from the rapid destruction of the damaged Rh-positive red cells that have been subjected to maternal antibody. Even the normal newborn infant has difficulty in disposing of bilirubin for the first several days of life, and this is markedly accentuated in the premature infant.[39] Since it has been shown that kernicterus is directly related to the level of bilirubin immediate exchange transfusion is indicated when hyperbilirubinemia is detected or impending. A bilirubin level of 20 mg. per 100 cc. should be considered the maximum permissible. This makes repeated exchange transfusions during the first forty-eight to seventy-two hours imperative if the bilirubin continues to rise rapidly; in some cases as many as three exchange transfusions have been necessary to maintain a bilirubin level of less than 20 mg. per 100 cc. until spontaneous clearing begins, usually by the third or fourth day.

It is believed that this policy of multiple exchange transfusions to control bilirubin increase has accounted for the great improvement in recovery rate and reduction in occurrence of kernicterus in infants with erythroblastosis fetalis. In fact, during the last four and a half years at the Richardson House of the Boston Lying-in Hospital, there has been no case of kernicterus since this method of management of the newborn infants was instituted, in contrast to a previous rate of 30 per cent. The technical details of the method of exchange transfusion through the umbilical vein were given in a previous communication.[40]

Breast feeding, even from a mother who has a high level of antibodies in her serum, is not contraindicated. Although, as Witebsky and Heide[41] originally showed, anti-Rh agglutinins can be demonstrated in the breast milk of such women, there is no evidence that these antibodies pass through the gastric mucosa after the child has completed the first two days of life.

Occasionally, an infant who has received one or more exchange transfusions is found to have a fairly severe anemia by the third or fourth week after birth. This is usually associated with a temporary physiologic inactivity of the bone marrow, with a low production of reticulocytes. Most such infants show a reticulocytosis (counts of 3 to 10 per cent or more) at about the fourth week, and specific supportive treatment is therefore unnecessary. If, however, the red-cell count falls below 2,000,000 and the infant begins to have anorexia, sleeplessness, increasing irritability or other signs of impending anoxia, a small transfusion of packed red cells (about 10 cc. per pound of body weight) may be given into one of the peripheral veins; this usually suffices to carry the infant beyond the period at which erythropoiesis is inadequate.

In a follow-up study of a considerable number of infants who have had erythroblastosis fetalis, with a comparison of their intellectual capacity with that of older siblings, we found no evidence of impairment of intelligence (or of motor ability). These infants had been observed closely, however, during the neonatal period and had given no clinical evidence of kernicterus during the first week of life. It is concluded that a baby with erythroblastosis who has been watched closely and who gives no signs of brain damage in the first week of life will show no late effects such as motor disability and mental retardation.

Summary

In the past ten years considerable advances in the knowledge of the Rh blood-group system have been made; these developments have been shown to possess both theoretical and practical importance. The discoveries made in the field of Rh are presented from the point of view of Fisher's hypothesis that the inheritance of the Rh system is determined by linked allelomorphic or alternative genes, in the belief that this theory enables the general reader more readily to understand the subject.

A full description of the new Rh antigen f is given; its practical importance is discussed, and consideration is given to the various genetic theories to explain its inheritance.

A brief account of recent progress in the management of clinical and laboratory problems associated with the Rh system is presented.

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MEDICAL INTELLIGENCE

MEDICOLEGAL ASPECTS OF THE WORCESTER TORNADO

F. H. Carr, M.D.*

WORCESTER, MASSACHUSETTS

LATE in the afternoon of June 9, 1953, Worcester was bringing to a close another humid industrial, business, agricultural and professional day. People, preparing to go home, paid the approaching storm little heed. As rain enveloped the city, they commented on the enormous size of the hailstones and sought shelter from them. But, not far out in the county, with no warning whatever, this ordinary storm was mysteriously metamorphosed into a more extraordinary bit of destruction than most communities have ever experienced. At one focal point, nature wrapped all its fury into one cataclysmic vortex. A tornado was born. Like a snowball rolling downhill, it gathered momentum and size. With devastating violence it struck a section of neighboring Holden and the northern portion of Worcester. Wooded areas were cut down, and dwellings were leveled. The air was filled with flying branches, beams, walls, roofs, furniture, automobiles and human bodies. The tornado then cut a narrow but deadly swath over hill and dale, demolishing a large new industrial building and then swooping down on a lumber yard. Rebounding next across a main highway, it wrecked the main building of Assumption College, laid waste a section of a new residential area and crumbled a large housing project and the Poor Farm. Without slackening speed, it continued its course through Shrewsbury.

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All these events took but a few minutes, but in those few minutes, Worcester County sustained millions of dollars in damage, hundreds of people were injured, and 88 of its citizens were killed or fatally hurt. Four months later, the area was still in the process of physical rebuilding; the last victim was discharged from the City Hospital on October 7.

The medicolegal chronicle of the Eleventh Worcester District began scarcely an hour later as dead bodies began to arrive at the city morgue, which is located in the City Hospital approximately 4 miles from the major disaster area and which was used as the base of operations by Dr. J. C. Ward, the medical examiner, and me. They arrived in all conceivable types of vehicles manned by volunteer corpsmen. As each body arrived, a numbered tag was attached to it. Tentative names and addresses, if known by the bearers, were written on these tags. The bodies were laid in rows that filled the floor of the morgue and, later, the adjoining corridor and hospital chapel. They were covered with sheets, except for the head and neck, which were cleaned as well as possible by members of the hospital nursing staff to facilitate identification. Many of these bodies were mutilated and practically naked, the clothing having been torn off by the force of the tornado. All valuables were left on the bodies.

Next, a second set of mortuary cards was numbered to correspond with the tags on the bodies. Then the diagnosis of the cause of death, which in most cases was readily apparent, as well as a list of valuables, was entered on these morgue cards.

Soon, anxious relatives, alerted by radio broadcasts, began appearing to identify missing persons. They were led on a guided tour of the morgue by Dr. Ward, myself and Mr. Matthew Carrigan, our assistant. I was able to identify 2 of my own patients.

When a positive identification had been made, the relative was instructed to engage an undertaker immediately and have him come to the morgue and remove the body. This was done because of the extreme overcrowding of the mortuary facilities.

When the situation was under control at the Worcester City Hospital, I made a tour of the other hospitals and carried out the procedure

effected at the city morgue, to which I then returned, since the majority of the victims were there.

Throughout the night people filed through the morgue on missions of identification. This was very difficult in some cases. A high school ring on one decapitated body cleared the identity. Two mothers claiming one child had their difficulty solved by a signet ring on the youngster's hand. At 2 a.m., because of beginning decomposition of the remaining bodies from the oppressive heat, civilian-defense authorities were consulted, and arrangements made for mass embalming of the unclaimed bodies. A squad of embalmers responded; the embalming was begun at about 5 a.m. and completed within a few hours. All but a few bodies were embalmed — these were so badly mutilated that the procedure was not feasible and they were placed in refrigerated compartments awaiting identification.

Incidentally, with an over-all hospital-bed population of approximately 3500 in Worcester, there is refrigeration space for only about 30 bodies. This made it all the more important for early identification and embalming to be done. At one time transfer of the unidentified bodies to a cold storage plant was considered but was not found necessary because rapid progress was made in the identification of the bodies, and mass embalming decided upon.

Newspaper reporters were allowed access to the morgue and to the tally sheets, but photographers were excluded. The Red Cross official list was corroborated.

On the following morning I went to Shrewsbury and Northboro, and Dr. Ward went to Holden and Jefferson to view the few bodies that had been taken to other hospitals and morgues in the district.

The afternoon and evening were spent back at the city hospitals and morgues to complete identification and proper care of the remaining bodies. Several calls were received from workers clearing away débris who thought that they had uncovered additional victims. Investigation disclosed that these were animal carcasses.

During the next several days bodies of those who had died in the various hospitals were also viewed. Identification of the last body was completed on the second day after the tornado. The last medicolegal case resulting from this disaster was examined on July 23, more than six weeks after the disaster.

This medicolegal survey includes only the Eleventh Worcester County District and therefore is not a complete picture of the disaster. There were several deaths in the adjoining districts.

The youngest victim of the tornado was a three-day-old male infant. His mother was considerably shaken up when her apartment was struck by the tornado at 5:20 p.m. She arrived at the hospital, the crown presenting on admission, and underwent a precipitous delivery at 7:15 p.m. without anesthesia. Autopsy revealed atelectasis, intracranial hemorrhage and congenital heart disease. Incidentally, the regular hospital pathologists performed all autopsies, patients dying after admission and treated in the hospitals being examined.

The oldest victim was an eighty-two-year-old man who died of a fractured skull.

The age groupings by decades are shown in Table 1. The preponderance of deaths among persons over fifty is readily explained by the fact that the disaster occurred in residential districts and at a time when most workers had not yet returned home. Many wives preparing supper were killed.

TABLE 1. *Age Grouping by Decades.*

DECADE	No. OF DEATHS
0–10	8
10–20	8
20–30	3
30–40	8
40–50	9
50–60	19
60–70	13
70–80	7
80+	3
Total	78

There were 43 females and 35 males.

The major causes of death are presented in Table 2. Most of the injuries were of a crushing nature. Except for burns and radiation injuries, the trauma sustained in this holocaust could not have been surpassed by atomic destruction. This is consistent with the recent report by the Boston Manufacturers Mutual Fire Institute of America, which stated that buildings, in the eye of the tornado, were subjected to 600 pounds of explosive pressure per square foot. This figure was based on the barometric drop from 15 to 11 pounds per square inch. Most factory buildings are constructed to withstand upward pressures of no more than 30 pounds per square foot, and ordinary homes even less.

TABLE 2. *Major Causes of Death.*

CAUSE OF DEATH	No. OF CASES
Fractured skull (most of these were depressed and many compound)	46
Fractured skull and crushing injury of abdomen	5
Fractured skull and crushing injury of chest	8
Decapitation	2
Crushing injury of chest and abdomen	9
Drowning (elderly people swept into lake by force of tornado)	2
Electrocution (lineworker, on following day)	1
Multiple fractures of long bones	1
Pulmonary embolism (death on July 23)	1
Coronary occlusion	1
Fractured ribs and coronary occlusion	1
Cerebral hemorrhage	1

In conclusion, the important medicolegal procedures in a disaster of this type appear to be

the proper tagging, diagnosing, identification and preservation of the bodies of the victims. The method described worked out extremely satisfactorily.

Dr. Ward and I are indebted to many medical examiners from other districts, who kindly offered their services to us in this emergency, and I am indebted to Dr. Ward for help in the preparation of this paper.

BY THE LONDON POST

Doctors — Supply and Demand

JOHN LISTER, M.D.

LONDON, ENGLAND

IN an address in 1895 at the opening of the new building of the Medical Faculty in McGill University (at that time only of college status), Sir William Osler remarked that it was no vain fancy that before the twentieth century was very old there might be effective vaccines against many of the contagious diseases. He went on to tell how a shrewd old fellow in contemplating this prophecy had said to him "Yes, many diseases are less frequent, others have disappeared, but new ones are always cropping up and I notice that there is not only no decrease but a very great increase in the number of doctors."

Nearly sixty years later the medical profession continues to increase in numerical strength, and the question of supply and demand is exercising the minds of medical-school authorities on both sides of the Atlantic. In this country the number of doctors has increased rapidly in recent years. The *Medical Directory* of 1939 showed the names of 37,429 physicians, and the same publication in 1952 listed 50,574 — an increase of 35 per cent. During the past six years the total number of registered practitioners in the United Kingdom has increased by about 1000 each year, and it is estimated that by 1960 there will be 1 doctor for every 800 persons in England and Wales. The *British Medical Journal* (in a leading article entitled "Too Many Doctors?") states that physicians seeking permanent positions are already finding it more difficult than formerly to get the jobs they want. There is no doubt of the truth of this claim because for every senior appointment, either in general practice or in the hospital service, there may be as many as 60 applicants and at present the number of advertised vacancies in either of these branches of medicine is small. Furthermore, the sharp division between consultant and general practitioner has made it important for the young doctor to choose at an early stage after graduation which line he proposes to follow. The man who chooses general practice must settle in practice as soon as possible after completing his intern year, for after that the longer he stays in hospital, the more difficult the entry into practice may be. This is perhaps because the man who lingers in junior hospital posts is suspected of having a consultant career as his first choice and no family doctor wants a partner who looks on general practice as second best. On the other hand the path to a consultant post is hazardous indeed: after many years in hospital as a registrar (resident), the prospective consultant must compete with 50 or 60 others for one of the few vacancies that arise. The chance of his failing to obtain a permanent post is great, and many fully trained physicians and surgeons cannot obtain consultant posts. For them the tragedy is that there is no line of retreat; the surgeons in particular have been trained for surgery and nothing else, and many are seeking employment overseas. Several factors have conspired to produce the present state of affairs, of which two may be specially mentioned: the fixing of definite establishments in the hospital service and the relative attractions of general practice and consultant or specialist work with particular regard to remuneration. In the early days of the National Health Service it was anticipated that there would be a demand for many more consultants. The remuneration of the general practitioner was so unattractive that large numbers of young men entered the field for training as consultants. Time has shown that not so many new consultant appointments were in fact required, and this experience, together with the need for financial economies in the National Health Service, has led to the creation of rigid hospital establishments. Thus, many of those in training are finding extreme difficulty in obtaining positions. The situation is bound to stabilize in time, and now that the general practitioners' financial prospects have been so much improved by the Dankwert's Award, the entry into this branch has been more sought after. Nevertheless, the General Medical Services Committee of the British Medical Association suggests that the Ministry of Health be asked to co-operate in the setting up of a working party. The task should be "to examine on a long-term basis and with the widest possible terms of reference the future number of medical practitioners likely to be required in all branches of the profession and to relate these needs to the intake of students to the teaching schools."

Taking up this subject in a leading article entitled "How Many Doctors?" the *Times* admits that by 1960 there may be 1 physician for every 800 persons in this country but points out that this ratio is the same as would obtain in the United States in 1960 if the expected population increase occurs and the number of doctors remains unchanged. The *Times* wonders, therefore, why the British Medical Association should view the figure with alarm, and even suggests that the *British Medical Journal's* leading article hints that official

medical policy would like to restrict entry into medical schools. In the concluding remarks it is stated that to examine solely the requirements in Britain constitutes too narrow an approach, and claims that the world needs more doctors especially in the undeveloped countries. This suggestion brought a smart retort from Dr. J. A. Pridham, chairman of the Committee on Medical Education of the World Medical Association, who points out that the World Medical Association has studied the problem and found that many nations are training more physicians than they can employ but that it is no solution for doctors to go to the undeveloped areas to practice. He states that the poorer countries cannot afford more doctors and that their available money is better spent on raising standards of nutrition, housing and hygiene. These countries prefer also to train their own nationals as physicians, seeking facilities in the medical schools of the highly developed nations. Speaking for this country alone, he considers that training surplus doctors in the hope that they will somehow, somewhere, find scope to practice is a waste of valuable resources.

An appropriate and not too serious postscript to these remarks on a provocative and important subject seems to be a story I heard from a colleague the other day. He was sitting on a committee to appoint a resident medical officer to a geriatric unit. All 3 applicants (not 60 here!) had been asked to be present for interview. The first was a married woman, who admitted that the appointment was attractive since it would not clash too much with domestic life; the second was a South African, who said that he had a calling to be a geriatrician and hoped to return to South Africa to preach the Geriatric Gospel; and the third, an octogenarian, claimed that he was fit for active employment and would gladly reside at the hospital, for he and his wife were seeking accommodation. His testimonial explained that his year of graduation was about 1895. The lay secretary of the committee whispered to the chairman that a polite way of turning down his application might be to offer him a bed instead of the job. Nevertheless, it looks as though geriatrics is still one of the few open fields.

MASSACHUSETTS PHYSICIANS ART ASSOCIATION

23. *New England Village*

First Prize, American Physicians Art Association, New York, 1953

Oil Painting by

ELIZABETH Z. KLEINMAN, M.D.

Assistant, Department of General Practice, New England Hospital

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40081

PRESENTATION OF CASE

First admission. A fifty-nine-year-old housewife entered the hospital complaining of stiffness and aching in the legs.

Four years before admission she began to have "rumbling" in her stomach. After three or four months watery diarrhea slowly started and increased to a peak of 8 to 10 stools a day two years before entry. The appetite decreased and the weight fell from the usual 170 pounds to 110 pounds. The stools never contained blood, pus or mucus, nor were they foamy or foul smelling. Two years before admission, x-ray studies showed multiple laminated gallstones by Graham test and normal esophagus and gastric rugae, with active peristalsis, after a barium meal. No gastric or duodenal defects were seen. After a barium enema the appearance of the mucosal pattern in the distal descending colon was somewhat irregular and suggested the presence of enlarged mucosal folds although it may have represented retained fecal material. One and a half years before admission she underwent cholecystectomy elsewhere and was placed on a bland, low-residue diet with phenobarbital and belladonna. She had only three stools a day then, two at night and one after breakfast. The stools were still watery and brown, however. She remained anorectic, with occasional vomiting. For the year before admission there were poorly defined aches, with stiffness in the lower extremities, in the neck and in the back with turning. These prevented easy ambulation. Six months before admission x-ray films of the spine, pelvis, feet and ankles taken elsewhere showed moderate osteoporosis and osteoarthritic changes. A gastrointestinal series was normal, and on barium-enema examination the barium passed to the cecum, with difficulty because of a voluminous colon. The colon was atonic except for intermittent spasm. No focal disease was seen. Sigmoidoscopic examinations were negative. The sedimentation rate was 22 mm. per hour; the white-cell count 12,800, and the hemoglobin 94 per cent (Sahli). The serum calcium was 10.7 mg., the phosphorus 2.7 mg., the alkaline phosphatase 14 Bodansky units, the serum protein 7.2 gm., the albumin 4.1 gm., the nonprotein nitrogen 35 mg., the cholesterol 365 mg., the fasting blood sugar 114 mg., and the bilirubin 0.5 mg. per 100 cc. A serum lipase was 1.0 cc. (0.05 N sodium hydroxide). The cephalin flocculation was negative. Stool examination showed no parasites, ova or enteric pathogenic bacteria. The urinary sediment contained 3 or 4 white cells per high-power field. The patient was given small doses of stilbestrol, with slight improvement in the aches of the legs. Because of persisting aches and stiffness, she was admitted for further study.

She had always lived in Boston and was happy with her four children. She had had an asymptomatic menopause at the age of fifty. For several years, there had been psoriatic lesions on the scalp, arms and back. Five years before admission urticaria developed during penicillin administration. She had urinary frequency (once or twice during the day and five or six times at night). She customarily drank milk with meals.

Physical examination revealed a moderately well nourished and well developed woman with dry, slightly pigmented skin showing psoriatic patches on the scalp, legs, buttocks and back. The axillary and pubic hair was scant. The chest had a few scattered rales that cleared with cough. The heart sounds were faint, but the rhythm regular. The abdomen was slightly distended, without tenderness and tympany. Peristalsis was normal. There was + ankle edema. Neurologic examination was negative.

The temperature was 98.6°F., the pulse 80, and the respirations 18. The blood pressure was 100 systolic, 65 diastolic.

The urine had a pH of 7 and a specific gravity of 1.012 and gave a ++ test for albumin and negative tests for sugar, bile and acetone. The sediment contained 2 white cells and frequent coarsely granular casts per high-power field. Examination of the blood revealed a white-cell count of 9300, with 77 per cent neutrophils, and a hemoglobin of 13.4 gm. per 100 cc.; the sedimentation rate was 6 mm. per hour. The serum calcium was 9.5 mg., the phosphorus 1.5 mg., the alkaline phosphatase 7.1 Bodansky units, the total protein 6.7 gm., and the albumin 4.7 gm. per 100 cc.; the serum chloride was 93 milliequiv., and the carbon dioxide 25.0 milliequiv. per liter. A bromsulfalein test showed 6 per cent retention of the dye in forty-five minutes, and the prothrombin time was 14 seconds (normal, 13 seconds). The serum vitamin A concentration was 1.9 units per cubic centimeter, with carotenoids of 1.8 units per cubic centimeter. The serum protein-

bound iodine was 6.8 microgm. per 100 cc. A stool examination showed slightly increased total fat and undigested muscle fibers, with normal neutral fats. The urinary calcium excretion was 181, 292 and 278 mg. per twenty-four hours on three tests. The Sulkowitch test was +++ to ++++. A phenolsulfonephthalein test demonstrated 20 per cent excretion of the dye in thirty minutes and 45 per cent in two hours. A chemical urinalysis disclosed no organic base, normal organic acids and high ammonia. X-ray films of the skull, spine and hands revealed moderately severe demineralization. The vertebral bodies lost some stature in the thoracic spine but none in the lumbar spine. The interspaces were of normal width, and there was no localized osteolysis. An upper gastrointestinal series was negative, and serial films showed the column of barium to reach the cecum in three and a half hours. The mucosal pattern of the jejunum and ileum was distinctly abnormal, with the appearance of increased prominence of the valvulae conniventes and some evidence of segmentation, especially in the ileum (Fig. 1). The findings suggested disordered motor function of the small intestines.

FIGURE 1. *Roentgenogram Taken An Hour after the Barium Meal, Showing the Stomach Almost Empty and the Head of the Column in the Lower Ileum.*
The mucosal folds are coarsened, and there is some barium flocculation.

When, on a second serum determination, a carbon dioxide of 19 milliequiv. and a chloride of 96 milliequiv. per liter were found, sodium citrate in doses of half a teaspoonful of 50 per cent solution was given four times a day. The urine pH remained at 6.0 and 6.5. The patient was discharged to continue sodium citrate, as well as folic acid, 20 mg. a day, and vitamin B_{12}, 30 microgm. twice weekly.

Final admission (eight months later). At this time she was admitted to the hospital because of an infection of the respiratory tract.

A few weeks after the previous discharge, the urinary calcium excretion was 180 mg. in twenty-four hours, and the serum carbon dioxide 21.6 milliequiv. and the serum chloride 92 milliequiv. per liter. Vitamin D, 50,000 units a day, with a high-calcium diet, was then started. Two months before admission sulfasuxidine, 0.5 gm. four times a day, was started, with immediate cessation of the diarrhea and improvement in the bone pains. When urticaria developed chlortetracycline was substituted, but the diarrhea returned. With sulfasuxidine and antihistaminic therapy there was no improvement. With this other medication, the patient felt better and walked with little pain. The serum calcium was 10.5 mg., the phosphorus 3.0 mg., and the alkaline phosphatase 4.4 Bodansky units; the serum carbon dioxide was 21 milliequiv., and the chloride 99 milliequiv. per liter. The urinary calcium excretion was 247 mg. in twenty-four hours. Three months before this admission, she had acute bronchitis and subsequently pneumonitis with pleurisy, which subsided slowly on chlortetracycline therapy. Three days before admission another respiratory-tract infection developed.

The physical findings were unchanged. The temperature was 97.8°F., the pulse 70, and the respirations 18. The blood pressure was 122 systolic, 66 diastolic.

On the second hospital day, she was found to be unable to move and was breathing shallowly but was able to follow objects with her eyes. She died a few minutes later.

DIFFERENTIAL DIAGNOSIS

DR. W. TREVOR COOKE*: The history at the first admission was quite noncontributory: the patient had diarrhea (8 to 10 stools a day), gallstones, a cholecystectomy and probably some mild indigestion. She began to have generalized aches and pains in the legs, which are quite commonly found with chronic diarrhea and are often associated with some degree of decalcification but give me no clue to the cause of the diarrhea. There was no mention whether or not the kidneys were affected at the time of admission to the other hospital. The only laboratory findings for comment are the slightly raised serum cholesterol, which I shall only mention to dismiss because I think it was within the normal range for a fifty-nine-year-old patient, and the slightly raised

*Reader in medicine, University of Birmingham, England; assistant physician, Queen Elizabeth Hospital.

fasting blood sugar, which may have some possible significance in the diagnosis of the cause of the diarrhea. It seems that the physicians in the other hospital attributed the osteoporosis to postmenopausal endocrine changes, and the patient was given stilbestrol, apparently with temporary improvement.

From the admission to this hospital I am given some clues about possible causes of the illness. I must consider the urinary calcium excretion of 181, 292 and 278 mg. per twenty-four hours, the slightly increased total fat in the stool, the relatively fixed urinary pH and specific gravity and the findings in the gastrointestinal series. Those major findings raise doubt whether this illness can be attributed to a single etiologic factor. Being interested in the intestinal tract, I immediately thought of sprue, the idiopathic variety, and almost immediately dismissed it. Certain features, the bone pains and diarrhea, would fit with idiopathic steatorrhea, as we tend to call the sprue syndrome in England, meaning that we do not know what causes it. Certain features do not exactly fit: in the uncomplicated sprue syndrome there is not a high urinary calcium excretion; there was no mention in the history of glossitis (it is rare in our experience not to find some reference to glossitis over a four-year period); and the blood counts can be considered normal. There was no mention of the appearance of the blood smears or of the mean cell volume so I assume that there was no significant change in spite of the fact that the patient was discharged on folic acid and vitamin B_{12}, which were given, I think, in the hope of influencing the mild fatty diarrhea rather than affecting the blood count. I shall rule out idiopathic steatorrhea at the moment.

Decalcification is also present with hyperparathyroidism and in the group of cases with hypercalciuria that seem treatable with albumin intravenously. To take the last group first the only patient of that type that I have studied certainly did not have any increased fat in the stools; there was an occasional attack of diarrhea. It has also been the experience of Dr. C. E. Dent[1] in 3 cases that there was no increase in fat in the stools. Hyperparathyroidism I must consider as a definite possibility though certain features are against it, such as the consistently low normal serum calcium; the phosphorus and alkaline phosphatase levels are consistent with such a diagnosis. I wonder if I might see the intestinal x-ray films before I go any farther?

DR. JOSEPH HANELIN: The examination of the upper gastrointestinal tract extended over about a six-hour interval. The stomach is not remarkable in appearance; its folds are within normal limits and it empties fairly promptly. The caliber of the small bowel is not increased, and the progress of the barium meal through the small intestine is only slightly if at all delayed. The mucosal pattern of the bowel, however, seems to be altered; the folds are coarsened and there is a suggestion of alteration of secretions within the lumen of the bowel (Fig. 1). We do not have the segmentation of the barium column, slow transit or dilatation of the small intestine that are commonly present with sprue.

DR. COOKE: Were these films taken with colloidal barium or with barium water?

DR. HANELIN: With barium water.

The films of the spine are normal except for the osteoporosis; there is no particular decrease in the height of the vertebral bodies. The hands show some degenerative arthritis and osteoporosis but none of the typical changes that are present in well established cases of hyperparathyroidism.

DR. COOKE: The intestinal x-ray films are compatible with the diagnosis of a deficiency pattern — using the term in the broadest sense — and that deficiency pattern may be present in the sprue syndrome. It is also seen in water and electrolyte deficiencies, in chronic nutritional disorders not primarily the sprue syndrome and to a certain extent in chronic pancreatitis though usually with some superimposed nutritional disorder.

We have now considered the possibility of sprue, hyperparathyroidism and the excessive idiopathic calcium-excretion syndrome — hypercalciuria. One must consider the tubular-dysfunction syndromes or chronic kidney disorders, which include the Fanconi syndrome and a number of other conditions, among which is excessive excretion or leak of phosphorus in the urine with osteoporosis. The absence of increased organic base and increased organic acids and possibly the presence of a high ammonia are against a gross tubular dysfunction. Furthermore, in the group of cases that Hunter[2] described, there was glycosuria, osteoporosis and low serum phosphorus; there was no indication of the presence of glycosuria or of an abnormality of the glucose metabolism in this case so that I do not think it falls into that group. In the 1 case of tubular dysfunction that we have studied[3] there was no intestinal dysfunction and no increase of fat in the stools. A point that is worth comment in cases of renal acidosis — using the term in the broad sense — is that the serum chloride is usually very high and the bicarbonate low. Here, the carbon dioxide was certainly low, but the chloride was not increased. I have been struck by such findings in chronic diarrhea; in other words in this patient there seems to have been an acidosis of intestinal origin rather than of kidney origin. The full explanation of this particular electrolyte pattern at the moment completely escapes me. It is evident that the possibility of a chronic acidosis, irrespective of its etiology, was in the minds of the physicians treating this patient when they started her on the citrate solutions. The treatment apparent-

ly had some effect in diminishing the rate of urinary calcium excretion.

I am still left "high in the air" about a possible diagnosis; my opinion is that hyperparathyroidism has to be included as probably the only way to explain the increased calcium excretion, that the kidneys themselves were damaged in the course of the hyperfunction and that there was possibly some chronic pyelonephritis as a result of that damage. Neither of those two conditions will account for the fatty diarrhea. I should like, therefore, to suggest that chronic pancreatitis was the cause of the mild fatty diarrhea. In such cases, if the condition is of long standing, there may also be osteoporosis. I am not prepared to say whether this or the associated parathyroid hyperfunction played the major role in the demineralization. With the vast majority of patients with chronic pancreatitis no hematologic abnormality is present. Whether parathyroid hyperplasia or parathyroid adenoma, I think possibly hyperplasia fits the best.

In the second admission the patient had much the same sort of findings. She had had some relief of bone pains with vitamin D, which many of these patients with both osteomalacia and osteoporosis have. She came in with an acute upper respiratory infection. One condition whose features were not stressed in this protocol and that one must consider in any chronic kidney and intestinal excretory upset is severe electrolyte depletion. A certain amount of this whole story was undoubtedly due to an electrolyte depletion, particularly potassium. I should like to hazard the guess that the cause of death was a low-potassium syndrome probably due to the excessive leak through the kidneys with the chronic pyelonephritis or loss through the intestinal tract or possibly both.

Dr. Benjamin Castleman: I must apologize to Dr. Cooke for asking him to discuss this very difficult case. After he had been chosen for the case I felt relieved when, in preparing for it, I found an article in the literature on osteoporosis with serum phosphorus written by Dr. Cooke and his associates.[3]

Dr. Jones, would you like to comment?

Dr. Chester M. Jones: I agree with Dr. Cooke that this is not the picture of sprue that we see in the hospital. It is obvious that the patient had a defect in small-bowel absorption that quite possibly could be explained by chronic pancreatitis of a low grade present for a long time; that, in turn, could explain the electrolyte changes. It is interesting that the other chemical determinations were not significantly out of order. There was no drop of serum albumin over the whole period, which is surprising with diarrhea producing any degree of malnutrition. I should imagine that this was a very complex situation in which the cause of the diarrhea was only one of the factors that produced the final picture.

Dr. Anne P. Forbes: I should like to add one or two items to the history. Dr. Cooke would be interested to know that repeated culture of the urine did not grow any organisms. Of course, as soon as we saw the albuminuria and the casts, we thought that she might have a chronic urinary-tract infection. I do not think the protocol quite brings out the dramatic response of the symptoms to vitamin D; that, of course, did not help us in the diagnosis. The phosphorus rose to normal, which is perhaps some help in the consideration of hyperparathyroidism; the phosphatase fell, and the bone pain was markedly improved. We should like to tell Dr. Cooke that normal serum calcium values are lower in this hospital than in many hospitals, so that the patient never had hypocalcemia according to our average normal value; the final calcium level of 10.7 mg. per 100 cc. was a rather high normal. About the potassium, it is dreadful that we did not do a potassium determination; her rapid downhill course was unexpected. She was admitted for a potassium determination and careful studies of the intestinal enzymes.

Dr. Fuller Albright: Because of the normal serum calcium, low serum phosphorus and high serum alkaline phosphatase, we arrived promptly at the diagnosis of osteomalacia. One can divide the causes of osteomalacia into two groups: one in which calcium absorption from the gastrointestinal tract is diminished (vitamin D lack and sprue) and another in which the calcium excretion in the urine is increased (renal tubular acidosis and Fanconi syndrome). Because of the long history of chronic diarrhea, we thought that the diarrhea must be the cause of the osteomalacia. We were surprised, however, to find such a high level of urinary calcium excretion. The response to vitamin D therapy tended to confirm the sprue theory. Because of the high urinary calcium excretion, we considered renal tubular acidosis. The serum carbon dioxide was slightly low on the first determination (25.0 mg. per 100 cc.) and decidedly low on the second (19.0 mg.); but the serum chloride was not high, which would be unusual with this diagnosis. We treated the patient with sodium citrate to overcome the acidosis. The giving of so much sodium citrate (1 teaspoonful of a 50 per cent solution four times daily) might have accentuated any potassium depletion present.

In summary we were not completely certain about the exact cause of the osteomalacia. I should like to ask Dr. Cooke a question about terminology. By osteoporosis, do you mean simply demineralization of the bone or do you refer to a specific type of demineralized bone?

Dr. Cooke: No; I was using osteoporosis as deproteinization of the bones and osteomalacia as demineralization. I mentioned both osteomalacia and osteoporosis because both occur in the sprue

syndrome. I think this particular patient probably had both.

DR. ALLAN M. BUTLER: The chemical analysis of the urine, I suppose, rules out tubular acidosis. Would Dr. Forbes agree?

DR. FORBES: I do not know that; we have not studied enough patients so that we can say that the chemical analysis of the urine rules out renal tubular acidosis. In about half our cases there was an unidentified organic base and a rather high organic acid in the urine.[4]

DR. BUTLER: Or else an inability to produce ammonia.

DR. FORBES: A diminished ability to produce ammonia so that less is produced for the same degree of acidosis. The urine was not suggestive of and the response to citrate was very unlike renal tubular acidosis. It would be interesting to know whether any serious pancreatic disease was observed at the time of the cholecystectomy.

DR. JOHN W. GAHAN: The cholecystectomy was done by the late Dr. Frank H. Lahey. Pancreatitis was not found at that time.

CLINICAL DIAGNOSES

Renal tubular acidosis.
Osteomalacia.
Potassium insufficiency.

DR. W. TREVOR COOKE'S DIAGNOSES

Chronic pancreatitis.
Hyperparathyroidism.
Pyelonephritis.
Potassium insufficiency.

ANATOMICAL DIAGNOSES

?Sprue.
Vacuolar tubular nephropathy, severe (probable potassium insufficiency).
Osteoporosis.
Parathyroid adenoma, microscopic.
Islet-cell adenoma of pancreas, inactive.
Thyroid adenoma, small.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: I do not know if I can solve all the problems in this case either. We first examined the gastrointestinal tract very carefully and found nothing abnormal grossly. Microscopical sections taken from many parts of the gastrointestinal tract showed slight hypersecretion and perhaps a little atrophy of the mucosa but nothing else. Of course this finding would fit in with the sprue syndrome. Some pathologists have described changes in the ganglion cells of the intestinal muscularis in the sprue syndrome; we have not observed any defect of the ganglion cells in this case or in others that we have had before. I am still unable to state what the cause of the diarrhea was, but I think it best fits in with the sprue syndrome.

The kidneys were quite unusual. The microscopical sections showed a very conspicuous change in

FIGURE 2.

the convoluted tubules. The epithelial cells were markedly enlarged and vacuolated. These vacuoles did not stain for fat or glycogen; in other words there was a watery replacement of the cytoplasm of the cells (Fig. 2). This picture was described a few years ago by Kulka, of our laboratory, and Pearson and Robbins,[5] of the Boston City Hospital, in 15 patients with intestinal disease. Ten of these patients had chronic ulcerative colitis; 2 had regional entertis, and the others had various other intestinal conditions, most of them with diarrhea. The authors were unable to explain this vacuolar nephropathy, but it appeared to be secondary in some way to the

intestinal disease. Since that publication, there has been some experimental evidence in animals[6] and an occasional report of a clinical case of diarrhea with the same renal picture, suggesting that it is probably due to potassium deficiency.[7,8] Both Dr. Cooke and Dr. Forbes suggested that potassium deficiency might have been the cause of this patient's death. It is quite likely that the patient had potassium depletion all along; unfortunately, no potassium determination was done during the first admission. We looked carefully in the heart muscle, which is another area in which the pathologist can detect potassium deficiency, but there were no detectable changes.

The bones showed a severe osteoporosis, not osteomalacia. There was no evidence of osteoid formation, but the good treatment with vitamin D and various other things over the eight-month period may have improved a pre-existing osteomalacia sufficiently so that no osteoid was left. In this section of the ilium (Fig. 3), one can see a paucity of bone trabeculae; those that are present are very thin and atrophic — the characteristic picture that we find in postmenopausal or any other form of osteoporosis.

There are a few other findings that complicated the picture. Sections of the four parathyroid glands were all perfectly normal except for a microscopic adenoma about 1 mm. in diameter in one gland. Whether this tiny adenoma in some way contributed to the hypercalciuria or low serum phosphorus I am not sure; I doubt if it did.

The other interesting finding was in the pancreas, which contained a large islet-cell adenoma measuring 7 cm. in diameter. This tumor was not an active insulinoma since the cells were all of the alpha type. To confirm our staining technic we sent some of the tumor to the Banting and Best Institute in Toronto, where an assay showed no activity. The tumor did not obstruct the pancreatic duct, and I do not believe the adenoma had anything to do with the present condition. In addition to the adenomas in the parathyroid and pancreas, there was a small one in the thyroid gland. Whether any of these adenomas had been active at one time and now were inactive, I do not know. One could call this case an example of the multiple-endocrine-tumor syndrome; occasionally in these cases there have been changes in the anterior pituitary gland.[9] Dr. Burt, will you tell us about the pituitary findings?

Dr. Agnes S. Burt: In this case the anterior pituitary gland was of normal size. In many of the cases of multiple adenomas that have been reported, the pituitary gland also contained adenomas of either the acidophil or chromophobe type. No adenoma was observed in the case under discussion, but there was hyperplasia of the sparsely granulated basophil cells, which had amphophilic staining properties and which on some previous work we have linked up with secretion of thyrotropic hormone and which therefore might tie up with the small adenoma in the thyroid gland.[10]

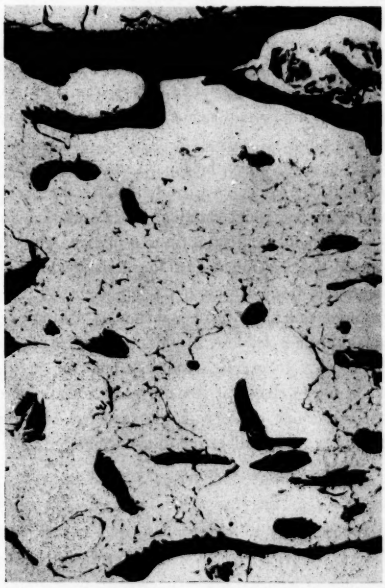

Figure 3.

Dr. Arnold S. Relman*: Dr. William Schwartz and I have had the opportunity of studying several cases clinically identical with the present case, but we have no information about the possible presence

*Associate member, Evans Memorial, Massachusetts Memorial Hospitals.

of endocrine tumors. Two of these cases were recently reported in detail.[11] All the patients had chronic diarrhea, which had resulted in severe chronic potassium depletion. In the 2 cases that we reported the diarrhea was proved to be due to chronic overuse of laxatives, and in the others it was attributed to nontropical sprue or chronic ulcerative colitis. In all these cases there was clear evidence of renal tubular dysfunction, including inability to concentrate the urine even after Pitressin injections and in some cases a low phenolphthalein excretion. In some cases we did specific renal-function studies and found reductions in TmPAH (transfer maximum para-aminohippurate), tubular extraction of PAH (para-aminohippurate) and renal oxygen consumption. The rate of glomerular filtration was also considerably reduced, but in only 1 of 4 cases was the blood nonprotein nitrogen significantly above normal.

In 3 cases in which the clinical situation was well controlled we were able to study the effects of treatment with potassium chloride. Renal function improved rapidly, and in 2 cases it became entirely normal. We therefore believe that renal dysfunction may result from chronic potassium depletion. We also think that these functional changes may in part explain certain features of this syndrome such as the inability to excrete alkaline urine even in the face of severe alkalosis. Renal dysfunction may also have something to do with the tendency of these patients to retain sodium and form edema.

The functional changes we have observed have their counterpart in the striking histologic changes in the kidney produced by potassium depletion. In the clinical literature there are at least 3 case reports of patients who died with severe potassium depletion and were found to have vacuolization of renal tubular cells quite similar to that reported by Follis et al.[6] in rats experimentally depleted of potassium. The lesions also resemble those described by Kulka and his associates[5] and by Jensen and his co-workers[12] in large groups of patients who died of chronic diarrheal diseases (unfortunately, no data on potassium metabolism were available in these cases).

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NEW ANTIBIOTICS

It is generally conceded that the antibiotics now available are highly effective in the treatment of a wide variety of infections and are responsible for the survival of many persons who would undoubtedly have died without their use. The tremendous output and sales of these antibiotics in the United States is ample proof of faith in their effectiveness for the treatment and prevention of serious infections even though much of this faith, particularly regarding many of the uses to which they are put, may in fact be unfounded. The tacit admission that many infections are still uncontrolled or inadequately affected is manifested by the tremendous efforts and investments still being expended by many commercial and other laboratories in the search for new antimicrobial agents. Nearly every one of the large manufacturers of pharmaceutic and biologic products is engaged in the search for new antibiotic agents.

The type of papers published in a recent issue of *Antibiotics and Chemotherapy* demonstrates that these efforts must be extensive indeed. Half the papers are devoted to observations on new antibiotics, but the reader need not be immediately concerned that he will soon be deluged with samples of all of them for clinical trial.

One of these papers, an abstract of material from a Ph.D. thesis, presents a clear example of the tremendous task confronting the various laboratories engaged in screening new and potentially useful antibiotics. In this small study alone 95 isolations of antagonistic bacteria were made from 80 soil samples. More than two thirds of the organisms isolated produced antibiotics that with the use of only 10 test organisms exhibited 35 different spectrums of activity. These represented the results of only crude tests, but the major work of determining their potential usefulness is so laborious and expensive that it could be carried out only by large manufacturers or endowed laboratories with extensive research facilities. In such laboratories thousands of organisms from samples of soil and from other types of material are continuously under investigation.

Of these new antibiotics only 2 could be considered potentially useful although some of the others may turn out to be so. One of the useful ones, tetracycline, has already been mentioned in these columns and is now available under the trade name of Achromycin. This antibiotic is an analogue of both chlortetracycline and oxytetracycline but lacks both the chlorine that characterizes the former and the OH group that characterizes the latter. Another antibiotic, which emanates from Belgium, has almost identical activity with erythromycin and carbomycin and may be the same as or a very close variant of one of these drugs.

Of the remaining agents described one is active against histoplasmosis in mice, but is said to be "too toxic for indiscriminate use in human histoplasmosis." Another, which is active primarily

against gram-positive organisms, produces hemolysis when given parenterally and thus has potential value only as a topical agent. A third, which is also active against gram-positive organisms and against protozoa in vitro, is too toxic to be considered for clinical trials. A fourth appears to be of interest, since it has a broad spectrum that embraces gram-positive and gram-negative organisms, large viruses and mycobacteria. Its low toxicity has permitted its use in laboratory animals in large doses, and it has proved far more effective against these experimental infections than could have been surmised from its antimicrobial activity in vitro. Of particular interest is its effectiveness against infection of mice with a virulent strain of tubercle bacillus and also with borrelia. Marked but irregular resistance can be induced in sensitive organisms with this agent in vitro though this feature appears to be irregular.

An additional agent, whose activity in vitro was high against gram-positive organisms and moderate against mycobacteria, but low against gram-negative organisms and yeasts, was presented. This drug appeared to give protection against infections with the hemolytic streptococcus in mice, for which it seemed to have low toxicity; it is still in the early stage of development, however.

The group of antibiotics discussed represented only a small distillate of the vast output in this field, although it may be considered perhaps to be the best that each of several laboratories has to offer from among the hundreds and perhaps even thousands of agents tested. Nevertheless, it is highly doubtful whether any of them, except tetracycline, which is already available, will ever become clinically useful on a wide scale. One should be grateful, however, to the manufacturers and research laboratories for continuing these intensive investigations, for there are still many areas in the field of infectious diseases that require effective therapeutic agents. This fact and the prospect of encountering progressively diminishing activity against many important infections by the antimicrobial agents now available warrant the sustained interest and activity in this highly important field.

UNSEATING THE SEATWORM

Increasingly, medicine moves forward along "a broadened front on which the laboratory or the clinic or the field have been brought together for the interpretation of a problem."[1] Exemplification of this multiple approach is afforded by Standen's[2] laboratory study of experimentally induced pinworm infection in mice and the clinical trial by White and Standen[3] of piperazine hydrate in treatment, as well as in the field studies of Weller and Sorenson[4] on the incidence and symptomatology of pinworm infestation in a group of 505 children — outpatients in a large metropolitan hospital.

In an effort to evaluate relative efficacy of gentian violet and piperazine hydrate in the treatment of pinworm Standen has taken the problem to the laboratory by testing the effects of the two drugs on "threadworm" infection (*Aspiculuris tetraptera*) in the mouse. Both medications given in tolerable, nontoxic doses had satisfactory therapeutic effects, and although gentian violet was found to be more efficient in clearing mice of parasites dose for dose, the decision to compare the therapeutic efficacy of the two drugs in children appeared justified.

In clinical trials, piperazine hydrate administered each day as a syrup containing about 50 mg. per kilogram of body weight was found to have a measurable vermicidal effect. When total daily dosage was increased from 100 to 250 mg. per year of life, the rate of cures was equivalent to that attained by gentian violet — about 70 or 80 per cent. White and Standen[3] reported that spontaneous cure of pinworm infection may be expected in 19 per cent of cases and that both piperazine hydrate syrup and gentian violet had marked vermicidal activity. Piperazine hydrate, however, was considered the drug of choice because of lack of toxicity and side effects, as well as ease of administration; of 31 children treated at levels greater than 50 mg. per kilogram of body weight daily (for a week and repeated after a week's rest) 97 per cent were cured.

Weller and Sorenson,[4] in a study undertaken more than a decade ago, found by use of perianal cellophane swabbing that 20 per cent of the outpatient population of a large children's hospital harbored pinworms and that the symptoms of infection were

so sketchy that the parasite could only be identified by search for the worm or its ovum. Moreover, because the incidence of such manifestations as anal pruritus, enuresis and loss of appetite was almost the same in children who gave evidence of infection as in those who did not, the authors concluded that although a large proportion of patients are practically asymptomatic subclinical infection is relatively common.

Recent studies by Bumbalo and his associates[5] confirm the widespread distribution of the parasite and the high incidence of infection among children and assert the general clinical importance of pinworm. Evaluation of four therapeutic agents was undertaken with oxytetracycline (10 mg. per pound of body weight, three times a day intracutaneously), resulting in a cure rate of about 80 per cent. The efficacy of oxytetracycline approximates that of gentian violet, and that of piperazine hydrate as reported by White and Standen.[3]

Thus the broadened front moves forward over the years even against the lowly *Enterobius vermicularis*. In the laboratory, in the clinic and in the field its enemy, man, relentlessly schemes its destruction, less from self-protection against a dangerous enemy — for there is little evidence that the tiny slug generally does much more than crawl about its own business — than as part of the war against filth, vermin and "ghoulies and ghosties, long-leggedy beasties and all things that go bump in the night."

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2. Standen, O. D. Experimental chemotherapy of oxyuriasis. *Brit. M. J.* **2**:757, 1953.
3. White, R. H. R., and Standen, O. D. Piperazine in treatment of threadworms in children: report on clinical trial. *Brit. M. J.* **2**:755-757, 1953.
4. Weller, T. H., and Sorenson, C. W. Enterobiasis: its incidence and symptomatology in group of 505 children. *New Eng. J. Med.* **224**:143-146, 1941.
5. Bumbalo, T. S., Gustina, F. J., Bona, J., and Oleksiak, R. E. Pinworm infection in children: comparative study of four oxyuricides. *Am. J. Dis. Child.* **86**:592-600, 1953.

"ELEVEN BLUE MEN"

Detective stories, universally popular, have an added interest if they are authentic; from a prejudiced professional point of view this is especially true if they concern matters of medical importance. *Eleven Blue Men and Other Narratives of Medical Detection*, recently published by Little, Brown and Company, is a volume of a dozen such tales. Most of them deal with the industrious efficiency of the New York Department of Health in tracking down the parasitic, bacterial or viral malefactors responsible for a series of assaults on the well-being of the world's largest city.

Not all the stories are in this category, however, for of the twelve one is a disquisition on gout, one an account of the rediscovery and commercial development of the antibiotics, one the story of eleven old men whose salt was savored with sodium nitrite in a lower Manhattan restaurant, and one the history of the famous Donora smog of October, 1948. All are examples of capable medical reporting by Berton Roueché; all appeared at one time or another in *The New Yorker*. Two — "A Pig from Jersey" and "The Fog" — won the 1950 Lasker Foundation Award for medical reporting.

Interesting as these stories are, their real significance lies in the fact that they represent an advance in what may be called the battle of medical communication. This is the battle to present accurately to the public — eager for news of health and of disease and its treatment and prevention — information that, until recent years, the medical profession has proudly withheld from it. But this attitude is changing. No longer is the clinic or the laboratory door slammed in the face of the trustworthy and discreet representative of a reliable newspaper. And a new breed of medical reporters is developing, like Mr. Roueché able to combine scientific accuracy with literary excellence.

THE LAHEY CLINIC

The name and genius of Dr. Frank H. Lahey was so identified with the institution he organized and developed that on his death there was naturally considerable interest within the medical profession regarding the future of the Lahey Clinic without the devoted guidance of its founder. It is assuring to know that the Clinic will continue unchanged, with the same organization and plans carefully conceived and carried out by Dr. Lahey.

In accordance with his expressed lifetime wishes Dr. Richard B. Cattell has been officially appointed as director and president of the Clinic. Dr. Cattell

also succeeds Dr. Lahey as surgeon-in-chief of the New England Baptist Hospital.

Also, in accordance with Dr. Lahey's plans, the Clinic was left to the Lahey Foundation, a nonprofit organization incorporated under the laws of the Commonwealth to undertake a variety of charitable, educational, public and scientific projects.

Recently appointed administrator of the Clinic is Dr. James E. Fish, who for the past eight years has served as medical director of the Ellis Hospital in Schenectady, New York.

The *Journal* extends its best wishes to the Clinic's new director and administrator.

Dysentery. — *However good ground there may be to suppose that the blood is contaminated by a telluric miasma, the truth of the supposition still remains absolutely uncertain, inasmuch as such supposed miasma is entirely beyond the circle of direct observation.*

Boston M. & S. J., *March 1, 1854*

MASSACHUSETTS MEDICAL SOCIETY

JOSEPH STANTON

1878–1954

The death of Dr. Joseph Stanton on January 3 deserves more than passing notice.

Born in Needham, Massachusetts, he received his degree *cum laude* from Harvard Medical School in 1903. He trained at Boston City Hospital and plunged into the practice of medicine with the enthusiasm that characterized him throughout life, carrying that enthusiasm, before long, into the specialty of general surgery.

Though his surgery embraced all but the central nervous system, he was never merely a surgeon. His treatment of the patient as a whole — his concern for the little things of importance — characterized his conception of the doctor-patient relation. It is doubtful if any physician ever inspired more complete confidence in his patients, a confidence that bordered on worship and flowed from his own self-confidence, which was expressed in the quiet, humble manner of one who was doing what had to be done.

Dr. Stanton was renowned as a speedy operator in a day when speed was important. This was because of his technical skill and deft hands combined with an inability to waste time or motion. The result was that, in the days before blood replacement was well developed, the number of operations he performed in a morning was amazing and the trauma to the patient minimal.

This ability never to waste time also allowed him, in spite of an unusually busy office and operating schedule, to make complete visits to his hospital patients and to keep up to date on both medical and good popular literature. He was also able to give proper attention to his family and to religious and civic duties.

He was a recipient of the honorary degree of Doctor of Laws from Boston College in 1914, and the Bene Merente Medal from Pope Pius XII in 1948.

Dr. Stanton was a member of the American Medical Association and a fellow of the American College of Surgeons. In 1953 he received a medal for fifty years' membership in the Massachusetts Medical Society.

He was a man of high character and extraordinary ability.

K. A. B.

DEATHS

ATWOOD — Charles F. Atwood, M.D., of Arlington, died on February 6. He was in his eightieth year.

Dr. Atwood received his degree from Harvard Medical School in 1900. He was an honorary member of the staff of Symmes Arlington Hospital and was formerly school and town physician and medical member of the Arlington Board of Health. He was a fellow of the American Medical Association.

He is survived by his widow, two sons, a sister and eight grandchildren.

BROWN — Josiah H. Brown, M.D., of West Newton, died on February 7. He was in his seventy-fourth year.

Dr. Brown received his degree from Jefferson Medical College of Philadelphia in 1917. He was formerly a member of the staffs of the Newton-Wellesley, Symmes Arlington and New York Lying-in hospitals.

He is survived by his widow and a son.

GUIDOTTI — Hugo G. Guidotti, M.D., of Hudson, died on January 4. He was in his fiftieth year.

Dr. Guidotti received his degree from Middlesex University School of Medicine in 1929. He was a member of the Massachusetts Society of Examining Physicians.

He is survived by his widow, one daughter and two sons.

JOUETT — Fred R. Jouett, M.D., of Cambridge, died on January 30. He was in his eightieth year.

Dr. Jouett received his degree from Harvard Medical School in 1899. He was a member of the American Heart Association and the New England Heart Association and a fellow of the American Medical Association.

He is survived by his widow.

NORMAN — Samuel P. Norman, M.D., of Malden, died on February 4. He was in his sixty-fourth year.

Dr. Norman received his degree from Boston University School of Medicine in 1916. He was senior obstetrician, Malden Hospital, and a member of the staffs of the Melrose, Whidden Memorial and Symmes Arlington hospitals and the New England Sanitarium, a fellow of the American Medical Association and a member of the New England Obstetrical and Gynecological Society.

He is survived by his widow, a son, a daughter, two brothers and two sisters.

BOSTON MEDICAL LIBRARY

"HISTORY OF MEDICINE"

In the December 19, 1953, number of *Minerva Medica* (published in Turin, Italy) Professor T. Oliaro has written an unusual short article on the history of medicine entitled, "The History of Medicine in Four Periods" (antique, medieval, renaissance and modern). It is illustrated with four full-size color plates. The first period features Esculapius, Imhotep, Hippocrates and Hammurabi, the second Roland of Parma, Galen and Avicenna, the third Leonardo da Vinci, Fracastorius, Tagliacozzi, Servetus and Harvey, and the fourth, the clinic, from Auenbrugger to Sydenham, and great physicians and scientists, from Malpighi, Roentgen and Virchow to Fleming. The four color plates are beautifully reproduced.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1954

Résumé

Disease	January 1954	January 1953	Seven-Year Median
Chancroid	4	3	3
Chicken pox	1466	4945	2391
Diphtheria	3	1	15
Dog bite	609	611	611
Dysentery, bacillary	60	13	10
Encephalitis, infectious	1	2	2
German measles	91	166	108
Gonorrhea	152	241	238
Granuloma inguinale	0	0	0
Hepatitis, infectious	103	108	4†
Lymphogranuloma venereum	1	0	1
Malaria	0	1	1
Measles	97	158	1167
Meningitis, meningococcal	6	11	7
Meningitis, Pfeiffer bacillus	6	8	5
Meningitis, pneumococcal	3	0	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	4	6	6
Mumps	1811	1098	1517
Poliomyelitis	9	6	2
Salmonellosis	44	12	4
Scarlet fever	487*	549	549
Syphilis	239	89	194
Trichinosis	7	1	1
Tuberculosis, pulmonary	194	169	198
Tuberculosis, other forms	13	6	12
Typhoid fever	1	0	0
Undulant fever	0	0	2
Whooping cough	166	136	408

*Includes streptococcal sore throat.
†Five-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, German measles, measles, scarlet fever and whooping cough.

The 1466 cases of chicken pox reported made this the lowest figure for the month of January since 1946.

The 97 cases of measles reported represented the lowest figure by a considerable margin for the month of January in the history of this state.

With one exception (1953) the figure of 166 cases of whooping cough reported was the lowest for the month of January in the history of the Commonwealth.

Diseases above the seven-year median included bacillary dysentery, infectious hepatitis, mumps, poliomyelitis and salmonellosis.

Bacillary dysentery and salmonellosis showed marked increases over the preceding month, and, in doing so, both established records for the month of January.

The figure of 9 cases of poliomyelitis reported was the highest for the month of January since 1931, and represented a carry-over from 1953.

Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Brookline, 1; Everett, 2; total, 3.

Dysentery, amebic: Milford, 1; Newton, 1; total, 2.

Dysentery, bacillary: Boston, 19; Cambridge, 2; Lowell, 1; Medford, 2; Worcester, 36; total, 60.

Encephalitis, infectious: Leominster, 1.

Hepatitis, infectious: Boston, 21; Brockton, 3; Cambridge, 11; Chelsea, 4; Concord, 1; Dedham, 1; Easton, 3; Fall River, 1; Fort Devens, 1; Framingham, 1; Franklin, 1; Hull, 1; Lenox, 1; Longmeadow, 2; Lynn, 19; Northborough, 2; North Brookfield, 3; Paxton, 2; Peabody, 1; Quincy, 1; Saugus, 2; Reading, 2; Springfield, 4; Waltham, 2; Watertown, 1; West Boylston, 1; West Springfield, 1; Worcester, 10; total, 103.

Meningitis, meningococcal: Boston, 5; Hingham, 1; total, 6.

Meningitis, Pfeiffer bacillus: Boston, 1; Braintree, 1; Georgetown, 1; Norwood, 1; Taunton, 1; Wellesley, 1; total, 6.

Meningitis, pneumococcal: Cambridge, 1; Fall River, 1; Lawrence, 1; total, 3.

Meningitis, mumps: Newton, 1; Walpole, 1; total, 2.

Meningitis, undetermined: Acton, 1; Springfield, 1; Weymouth, 1; Worcester, 1; total, 4.

Poliomyelitis: Arlington, 1; Beverly, 1; Boxford, 1; Granby, 1; Marblehead, 1; Pittsfield, 1; Salem, 1; Westford, 2; total, 9.

Psittacosis: Holyoke, 1; South Hadley, 1; total, 2.

Salmonellosis: Attleboro, 1; Boston, 1; Brookline, 3; Cambridge, 28; Clinton, 2; Milford, 2; Newton, 3; North Andover, 1; Watertown, 1; Wellesley, 1; Winchester, 1; total, 44.

Trichinosis: Boston, 3; Newton, 1; Scituate, 3; total, 7.

Typhoid fever: Northampton, 1.

CORRESPONDENCE

ACKNOWLEDGEMENTS OF ASSISTANCE

To the Editor: In our article, "Bed Rest in the Treatment of Pulmonary Tuberculosis," in the January 14 issue of the *Journal*, we regret very much that certain acknowledgements of assistance in the completion of the study were omitted entirely by error. We are indebted to Drs. Sidney L. and Harvey R. Morrison, roentgenologists of the Channing Home, not only for their advice and guidance in x-ray interpretation but also for their many years of service to the institution, and to the Morrison Office staff for their co-operation and help in assembling the x-ray films and making space available for the comparative x-ray analyses.

Miss Elizabeth Pelton, superintendent of the Channing Home, played a very important role throughout the period of the study by her supervision of the regimen of "strict bed rest." Owing to her genius and wisdom in the handling of patients she and her staff of nurses were the ones who carried out the treatment and made a program of "strict bed rest" possible.

Albert I. DeFriez, M.D.
William E. Patton, M.D.
Edward J. Welch, M.D.
Theodore L. Badger, M.D.

Boston

REGARDING POLIOMYELITIS VACCINE

To the Editor: The editorials in the October 3, 1935, and the March 19, 1936, issues of the *Journal* warned against the too hasty trial of vaccines advocated for the prevention of anterior poliomyelitis. Grave doubts about the safety of the vaccines were expressed.

I wonder if the *Journal* is giving unqualified approval of the Salk vaccine despite the tragedies caused by the Brodie and Kolmer vaccines in 1935. I understand that no human controls have been run with the Salk vaccine. Its effective-

ness is evidently based merely on animal experiments and the fact that it raises the titer of the antibodies in human beings to whom it is given. Aycock and Hudson (*New England Journal of Medicine* **214**:715-718, 1936) found a considerable increase in immunity in both vaccinated and unvaccinated controls, that is, 19.3 per cent against 14.9 per cent. Kramer (*Journal of Immunology* **31**:167, 1936) observed neutralizing antibodies in 50 per cent of vaccinated children and 41 per cent in the control group. Neither of these studies considered the small differences of any practical value in favor of the vaccinated group.

Kramer points out that, from a public-health point of view, it is questionable whether it would be a good procedure to immunize thousands of persons, who would escape the disease, to protect the few who would be crippled by it. The accidental development of one case of poliomyelitis from the vaccine in several hundred or even a thousand, according to Kramer, would approach the incidence of the disease and thus negate any value that might accrue. Van Rooyen and Rhodes, in their book, *Virus Diseases of Man* (page 1016), warn against the use of any poliomyelitis vaccine.

I have learned, much to my amazement, that, of the 58,000 cases of poliomyelitis in the United States in 1952, virus recovery tests were made in only about 1 per cent. It is merely assumed then that the other 99 per cent were caused by a virus. Yet we hope to eliminate poliomyelitis by means of a vaccine when we do not know what causes all cases of human poliomyelitis. Is this not contrary to Koch's first postulate, in which he stresses that the agent must be found in every case of the disease?

I should like very much to know how the *Journal* has reacted to the claims for the Salk vaccine in view of its reactions to the Brodie and Kolmer vaccines of two decades ago.

RALPH R. SCOBEY, M.D.

Syracuse, New York

Note: An editorial on this subject appeared in the *Journal* on February 11.—ED.

NOTICES

BOSTON MEDICAL HISTORY CLUB

A meeting of the Boston Medical History Club will be held in the Boston Medical Library on March 1 at 8:15 p.m. Dr. Leo Alexander will speak on the topic "The Commitments and Suicide of King Ludwig of Bavaria." Books on the subject will be exhibited.

CHELSEA SOLDIERS' HOME STAFF MEETING

There will be a professional staff meeting of the Soldiers' Home, Chelsea, in the Quigley Memorial Auditorium, on March 8 at 8:15 p.m. Dr. Richard Ford, assistant professor of legal medicine, Harvard Medical School, and pathologist, Massachusetts Department of Public Safety, will speak on the topic "Investigations of Violent Deaths." All physicians are invited.

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE SPRINGFIELD CHAPTER

A meeting of the Greater Springfield Chapter of the Massachusetts Academy of General Practice will be held in the staff room, Mercy Hospital, Springfield, on March 3 at 8 p.m. Mr. Thomas McElhone, welfare agent of Springfield, will speak on the topic "Problems of the Welfare Patient" at 9:15 p.m. Nonmember physicians are invited to the lecture.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A meeting of the Middlesex South District Medical Society will be held in Margaret Jewett Hall, Mount Auburn Hospital, Cambridge, on March 10 at 8 p.m. Dr. Francis D. Moore will speak on the topic "The Management of Acute Emergencies Arising in Surgical Care." The discussers will be Drs. Joseph A. Holmes, Lewis S. Pilcher and John B. Vernaglia.

NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held on Wednesday, March 10.

11:00 a.m.–12:00 m. Morning session (conducted by Dr. Janeway and staff). Auditorium, Jimmy Fund Building.

12:00 m.–1:00 p.m. Clinicopathological conference (conducted by Dr. Farber). Auditorium, Jimmy Fund Building.

2:15–4:30 p.m. Scientific session (conducted by Dr. Allan M. Butler). Auditorium, Jimmy Fund Building.

5:30–7:30 p.m. Refreshments and dinner, Longwood Towers, Brookline.

7:30 p.m. Business meeting. Auditorium, Jimmy Fund Building.

7:45 p.m. The Movement of Infectious Agents in the Body. Dr. Paul B. Beeson, professor of medicine, Yale University School of Medicine.

SEMINAR AND CONFERENCE ON CANCER CYTOLOGY

The third annual Seminar and Conference on Cancer Cytology will be conducted by the Cancer Institute at Miami, April 21–24. The latest advances in cancer diagnosis, using new cytologic methods and blood-testing procedures, will be presented. The program is under the direction of Dr. J. Ernest Ayre.

SOCIETY MEETINGS AND CONFERENCES

MARCH 1. Boston Medical History Club. Notice above.

MARCH 1 and 15, APRIL 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

MARCH 1–31. Consultation Clinics for Crippled Children. Page 305, issue of February 18.

MARCH 2, 9, 16, APRIL 8 and 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.

MARCH 3. Massachusetts Academy of General Practice. Springfield Chapter. Notice above.

MARCH 3 and APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

MARCH 8. New England Cardiovascular Society. Page 304, issue of February 18.

MARCH 8. Chelsea Soldiers' Home. Staff Meeting. Notice above.

MARCH 9. Harvard Medical Society. Page 304, issue of February 18.

MARCH 10. New England Pediatric Society. Notice above.

MARCH 10. Middlesex South District Medical Society. Notice above.

MARCH 11–13. American Orthopsychiatric Association. Page 129, issue of January 21.

MARCH 12–MAY 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

MARCH 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

MARCH 20, APRIL 17 and MAY 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.

MARCH 22–25. American Academy of General Practice. Page 129, issue of January 21.

MARCH 24. Middlesex East District Medical Society.

MARCH 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

MARCH 28. National Gastroenterological Association. Page 265, issue of February 11.

MARCH 31–APRIL 2. American College of Surgeons. Sectional Meeting. Page 266, issue of February 11.

APRIL 7. Massachusetts Academy of General Practice. Spring Clinical Assembly, New Bedford.

APRIL 8–11. International Academy of Proctology. Page 130, issue of January 21.

APRIL 9. New England Society of Anesthesiologists. Page 87, issue of January 14.

APRIL 10. American Congress of Physical Medicine. Page 266, issue of February 11.

APRIL 21–24. Seminar and Conference on Cancer Cytology. Notice above.

APRIL 29, 30 and MAY 1. American Goiter Association. Somerset Hotel, Boston.

MAY 11. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)

MAY 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.

MAY 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

MAY 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JUNE 17–19. American Geriatrics Society. Page 266, issue of February 11.

JULY 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

(Notices concluded on page xxi)